| | |
|---|---|
| NDA: 18-859 | TRADE: VIRAZOLE AERO. |
| SPONSOR: VIRATEK INC. | GENERIC: RIBAVIRIN |
| APPROVAL LETTER: Y | STATISTICIAN'S REVIEW: Y |
| SBA: Y | BIO/DISSOLUTION REVIEW: Y |
| FINAL PRINTED LABEL: Y | MICROBIOLOGIST'S REVIEW: N |
| MEDICAL OFFICER'S REVIEW: Y | NAC/NRC REVIEW: N |
| CHEMIST'S REVIEW: Y | FEDERAL REGISTER NOTICE: N |
| PHARMACOLOGIST'S REVIEW: Y | DATE: 06/25/87 |


APRVL
LTR

DEC 31 1985

NDA 18-859

Jeffrey Steffa, Ph.D.
Viratek, Inc.
3 [illegible]0 Hyland Avenue
Costa Mesa, California 92626

Dear Dr. Steffa:

Please refer to your New Drug Application dated September 21, 1982 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Virazole (ribavirin) Aerosol.

We acknowledge receipt of your December 17, 1985 submission that includes your agreement to conduct the post-marketing studies delineated in our December 16, 1985 letter and your assurance that lots BV-VR-1 and BV-VR-2 will not be distributed.

We have completed our review of this application as amended and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included in the submission dated December 28, 1985. Accordingly, the application is approved.

Please submit one market package of the drug when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.30 and 314.81 for an approved NDA.

Sincerely yours,

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: SAN-DO
ORIG. NDA 18-859
HFN-82
HFN-710
HFN-220
HFN-800/JMinor
HFN-815
HFN-815/MO
HFN-815/PHARM
HFN-815/CHEM
HFN-815/JKnight/12/24/85/tcd/12/26/85
R/D Init. by: GRStanley for ETabor/12/31/85
F/T: 12/31/85
0216u

APPROVAL

SBA

SUMMARY OF BASIS OF APPROVAL

NDA 18-859

Applicant:
Viratek
Costa Mesa, CA 92626

Drug Generic Name:
Ribavirin

Drug Trade Name:
Virazole Aerosol

I. Indications and Usage:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease. Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that
is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

II. Dosage Form, Route of Administration and Recommended Dosage:

Virazole is supplied as lyophilized drug to be solubilized with sterile water for injection or sterile water for inhalation and administered as an aerosol using the Viratek Small Particle Aerosol Generator (SPAG), Model SPAG-2.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed. However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation.

Six grams of lyophilized drug are solubilized with sterile water for injection or sterile water for inhalation to a final volume of 300 ml (drug concentration 20 mg/ml). Using this drug concentration as the starting solution in the drug reservoir of the SPAG-2 unit, the average aerosol concentration for a 12-hour period is 190 micrograms/
liter of air.

III. Manufacturing and Controls:

Manufacturing and controls, stability, methods validation, labeling, inspections and environmental impact evaluation conform to all federal regulations.

IV. Pharmacology:

Ribavirin, a synthetic nucleoside analog, is active in vitro against a number of viruses, including RSV. This activity is thought to be related to the effects of its phosphorylated derivatives (formed intracellularly) upon enzymes involved in nucleic acid synthesis (ribavirin 5'-phosphate inhibits IMP dehydrogenase; ribavirin triphosphate inhibits RNA polymerase and guanylyl transferase).

The acute oral $LD_{50}$ of ribavirin is reported to be 2 g/kg in the mouse and 4-5 g/kg in the rat. However, in a subacute study, a daily oral dose of 80 mg/kg was lethal to rats, 30% of the animals succumbing after 3-4 weeks of treatment.

Anemia was the most common ribavirin toxicity in oral animal studies; it occurred in all species tested. Bone marrow findings ranged from erythroid depression to marrow atrophy. Normochromic macrocytic anemia (accompanied by thrombocytosis at the higher doses) was observed in parenterally-treated rhesus monkeys. Other drug-related toxicity included enteropathy (dog, rhesus monkey), myocarditis (rat), lymphoid atrophy (rat, rhesus monkey), and liver toxicity (rat, squirrel monkey).

Inhalation toxicity studies were performed in adult rats, mice, and squirrel monkeys. In rats, ribavirin aerosol exposure (12 hours/day) resulted in a high mortality rate at dose levels above 22 mg/kg/day. Lung histopathology included alveolar edema and hemorrhage, as well as hypertrophy and hyperplasia of alveolar cells. Also, at all dose levels, there was increased accumulation of foam cells in the alveoli. Other pathology in ribavirin aerosol-treated rats included inflammation of the myocardium and epicardium, often associated with myocardial necrosis and interstitial edema. No lung lesions related to drug treatment were observed in mice exposed to ribavirin aerosol 12 hours daily for 28 days at 30 mg/kg. At higher dose levels, all mice died within the first week or two of treatment. Although there was no drug-related lung pathology, systemic lesions resembled those in other animal studies (e.g. enteropathy, bone marrow hypocellularity); multifocal mineralization of the heart was found at all dosage levels. In squirrel monkeys, 4 days of continuous exposure at 40 mg/kg/day, resulted in no pulmonary pathology, but there was centrilobular fatty change in the livers.

The effect of ribavirin aerosol on the developing lung in animals has not been fully evaluated. A study in newborn ferrets revealed the difficulty in the design of such a study. The results, although inconclusive, suggest that ribavirin inhalation can lead to inflammatory, proliferative, and emphysematous changes in the lungs of these animals. The manufacturer has made a commitment to conduct another study of this type in a different species in the near future.

Ribavirin has shown evidence of teratogenic and/or embryocidal activity in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in various animal studies. Survival of fetuses and neonates was reduced. The drug was embryolethal in rabbits at daily oral dose levels as low as 1 mg/kg.

Ribavirin produced testicular lesions (tubular atrophy) in adult rats treated long term at oral dose levels as low as 16 mg/kg/day (lower doses were not tested). The fertility of ribavirin-treated animals (male or female) has not been investigated.

Ribavirin has been shown to be mutagenic to mouse lymphoma (L5178Y) cells in culture. However, results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative. Ribavirin induces cell transformation in an in vitro mammalian system (Balb/C 3T3 cell line). Incomplete results of carcinogenicity studies suggest that chronic feeding of ribavirin to rats (16-60 mg/kg body weight daily) can induce benign mammary, pancreatic, pituitary and adrenal tumors.

V. Medical:

A. Clinical Studies, Efficacy:

1. A placebo-controlled, randomized, double-blind study conducted by Taber et al. at Baylor University from 1981-82 demonstrated efficacy in infants with bronchiolitis due to RSV infection (Pediatrics 1983; 72:613). Infants included in the study had been born at full term, had no underlying cardiac or pulmonary disease, and had positive RSV cultures from nasal secretions. Twelve infants (4M, 8F) were included in the ribavirin group and 14 (10M, 4F) in the placebo group. The mean age of patients in the ribavirin group was 3.9 ± 3.3 (S.D.) months and that in the placebo group was 3.7 ± 2.9 (S.D.) months. The average duration of illness prior to admission in the ribavirin and placebo groups was 35.2 hours and 50.4 hours, and the average time from admission to starting treatment was 9.1 hours and 8.9 hours. Ribavirin or the placebo saline solution was administered as an aerosol at the rate of 12.5 L/min for about 12 hour/day beginning within three days of onset of the bronchiolitis. The initial concentration of ribavirin in the aerosolizer solution was 20 mg/ml. The average duration of treatment was 79.1 hours in the ribavirin group and 76.0 hours in the placebo group.

Efficacy was evaluated by a bronchiolitis score, which was based on a daily clinical summary of the severity of illness as assessed on a scale of 0 to 3+ (0 = normal, 3+ = most severe). At baseline, the mean bronchiolitis score was 2.0 in both the ribavirin and placebo groups. By the third treatment day, the bronchiolitis score was significantly lower in the ribavirin-treated patients (0.6 vs 1.3, P = .044, Wilcoxon rank sum test, two tailed; see Table 1).

There were no statistically significant differences between the ribavirin and placebo groups with respect to length of treatment, time from onset to discharge and

time from end of treatment to discharge. The mean RSV titers in nasal wash specimens ($log_{10}$, half the tissue culture infectious doses per milliliter of original nasal wash or $TCID_{50}$/ml) in the ribavirin and control groups were 3.0 and 2.6 at day 0 and were 0.9 and 1.0 at day 3 (differences not statistically significant).

2. Hall et al. conducted a randomized, double-blind, placebo-controlled study that demonstrated the efficacy of ribavirin in the treatment of infants with lower respiratory tract infection due to RSV at the University of Rochester in 1982-83 (New Engl. J. Med. 1983; 308: 1443). This study will be referred to as the Hall 1 study. The study included 16 infants in the ribavirin group (13M, 3F) and 17 in the placebo group (8M, 9F). Infants admitted to the study had lower respiratory tract infection proven to be caused by RSV (by immuno-fluorescent-antibody testing and viral isolation), and they were judged ill enough to require at least three days of hospitalization. Infants with significant underlying disease were excluded.

The median age of patients in the ribavirin group was 13 weeks and in the placebo group was 10 weeks. Premature infants were not excluded. The mean duration of illness prior to admission in the ribavirin group and in the placebo group was 2.9 days and 3.2 days, respectively, and the mean duration time from admission to starting treatment was 1.6 days and 1.4 days.

Ribavirin solution (20 mg/ml) or water was administered as an aerosol at the rate of 12.5 L/min into an infant oxygen hood, tent, or the inhalation tubing of a ventilator. Aerosolization was continued for an average of 20 hours per day and for a minimum of three days. The average duration of treatment was 4.9 days in the ribavirin group and 4.7 days in the placebo group.

Efficacy was assessed by a daily rating of the severity of the illness and the child's general status (illness severity score) on a scale from 0(normal) to 4+(most severe). On admission, the illness severity score was 3.1 in the ribavirin group and 2.8 in the placebo group. By treatment day three, the severity score was 0.9 in the ribavirin group and 2.1 in the placebo group (see Table 1), which is a statistically significant difference at P less than 0.01 using the Mann-Whitney U test and Student's t-test.

The results of viral cultures of nasal-wash specimens taken after aerosol therapy had been interrupted for periods of 1 to 3 hours are also shown in Table 1. The amount of virus detected in the washings of patients treated with ribavirin was significantly less than that from patients in the placebo group by the third treatment day. The average number of days of RSV shedding from the start of therapy was 2.9 days in the ribavirin group and 4.5 days in the placebo group (P less than 0.003 by Student's t-test and Mann-Whitney U test).

3. Hall et al conducted a randomized, double-blind, placebo-controlled study of ribavirin in infants with proven lower respiratory tract infection due to RSV in 1983-84. This study will be referred to as the Hall II study. It was published with a somewhat larger data base as a report in the Journal of the American Medical Association (1985; 254:3047). The study as reported in the NDA included 12 infants in the ribavirin group and 10 in the placebo group. The study design was similar to the Hall I study except that patients with broncho-pulmonary dysplasia and/or congenital heart disease were not excluded and about half the patients admitted were in this category. The mean age of the infants was about 15 weeks, and the mean duration of illness prior to treatment was approximately five days in both the ribavirin and placebo groups.

Ribavirin and placebo (water) aerosols were administered as in the previous study. Clinical efficacy was assessed by a daily rating of the overall severity of the illness on a scale from 0 (normal) to 10 (most severe). At the time treatment was started, the mean illness severity score was 6.1 in the ribavirin group and 4.5 in the placebo group (P = .067). At the end of treatment (about 5 days), the severity scores were 3.0 and 3.3 in the ribavirin and placebo groups. Although the incremental improvement over the treatment period was significantly greater for ribavirin (3.0 vs 1.2, P = 0.007), little weight is given to these results in support of efficacy because of the disparity in the severity scores between the two groups at baseline.

The results of viral cultures of nasal-wash specimens support the conclusion that ribavirin decreases virus shedding in these patients (see Table 1). The amount of virus detected in specimens from patients in the ribavirin group was significantly less than that from patients in the placebo group at days 4 and 5.

4. Additional support for the efficacy of ribavirin for RSV infection is provided by the results of a randomized, double-blind, placebo-controlled study conducted by Hall et al. in experimentally infected adult volunteers (JAMA 1983; 249:2666). Sixteen healthy adults (13M, 3F) between the ages of 20 and 30 years received 5 $\log_{10}$ $TCID_{50}$ of RSV intranasally. They were randomly assigned to receive either ribavirin or placebo (water) aerosol starting 2 days after the RSV innoculation and continuing for 3 days, 12 hours daily. The aerosol was administered at a rate of 12.5 L/min through a face mask and the concentration of ribavirin in the liquid reservoir was 20 mg/ml.

Clinical effects assessed were minor symptoms, systemic symptoms, and fever. Subjects were examined twice daily and were questioned for signs or symptoms of respiratory illness or systemic complaints, which were graded 1+ to 3+ according to severity. Minor symptoms included rhinitis, sore throat, lymphadenopathy, and sneezing, while systemic symptoms included general myalgia, malaise, anorexia, nausea, or symptoms of tracheo-bronchitis. Points were assigned by giving minor symptoms the same rating as the severity grading (1, 2 or 3) while systemic symptoms were rated as 2 points for 1+, 4 points for 2+, and 6 points for 3+ severity. Oral temperatures were measured three times daily. Temperatures in the 37.5 to 37.7$^{o}$C range were rated as 3 points, those in the 37.8 to 38$^{o}$C range as 5 points, and temperatures above 38.1$^{o}$C as 7 points.

Seven subjects in the placebo group and 6 in the ribavirin group were shown to be infected with RSV by detection of viral shedding in the nasal wash. Twelve of the 13 infected subjects manifested signs or symptoms of upper respiratory tract illness. The results of the clinical evaluation are shown in Table 2. The average score for minor symptoms was higher in the ribavirin-treated group although the difference was not statistically significant. However, the average scores for systemic symptoms and for fever were significantly lower in the ribavirin group, thus suggesting that the drug lessened the more severe manifestations of experimentally-induced RSV infection.

B. Clinical Studies, Safety

A total of 320 infants and children received ribavirin aerosol therapy, which included 109 in clinical studies and 211 as "compassionate" treatment cases. Eighty-four adults also received ribavirin aerosol: 61 in clinical studies of influenza, 20 in tolerance studies among healthy and pulmonary-compromised volunteers, and 3 as "compassionate" treatment cases with severe influenza infections.

Ribavirin aerosol was generally well-tolerated in patients with no underlying lung disease who did not require assisted ventilation. Among the 109 patients who received ribavirin aerosol and the 93 control patients in the pediatric clinical studies, the incidence of vomiting and diarrhea was similar in both groups (7-10%). Cyanotic episodes were reported in 3 ribavirin-treated and in 7 control patients, and 2 patients in each group were reported to have had apneic episodes. Conjunctivitis was reported in 5 ribavirin-treated and 3 control patients, while more cases of skin rash were reported in the control patients (1 vs 10). There were no deaths among the pediatric patients in clinical studies.

Although anemia was not reported with use of ribavirin aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol were not evaluated 1 to 2 weeks post-treatment when anemia is more likely to occur. Reticulocytosis was reported infrequently with the aerosol.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. Most of these patients were "compassionate" treatment cases, and the role of ribavirin aerosol is indeterminate. Pulmonary events included worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence. Cardiovascular events included cardiac arrest, hypotension, and digitalis toxicity.

Some subjects requiring assisted ventilation have experienced serious difficulties that may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted. The labeling contains a boxed warning at the beginning of the labeling with the following statement in boldface type:

RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.

Twenty-two deaths occurred among the 211 pediatric, "compassionate" treatment cases; 13 occurred during ribavirin treatment and 9 occurred within 2 to 18 days after ribavirin was discontinued. All but one of the deaths occurred in patients with significant underlying disease. One of the deaths was considered possibly-related to ribavirin. A four-month old male infant with pulmonary stenosis and a Waterston shunt was diagnosed as having RSV pneumonia. The patient was on a respirator and within one hour of ribavirin aerosol treatment, he was wheezing, cyanotic, and had mottled skin. Ribavirin crystals were noted in the endotracheal tube. Wheezing was unresponsive to bronchodilators. After 10 hours, ribavirin was discontinued and within one hour the patient's wheezing improved. Five days after ribavirin was discontinued, the patient died with multiple organ system failure (CNS dysfunction secondary to renal and hepatic failure, deteriorating cardiopulmonary function).

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in 6 of 6 adults with chronic obstructive lung disease and in 4 of 6 asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

VI. Post-Marketing Surveillance, Phase IV Studies

In addition to the usual monitoring of spontaneous reports from the field, the following will be conducted:

A. Follow-up pulmonary function testing at age 4-6 years of patients who received ribavirin or placebo aerosol in infancy;

B. Observation for in vitro and in vivo drug interactions between ribavirin and frequently used concomitant medications such as antibiotics, digitalis, or bronchodilators;

C. Monitoring for the development of ribavirin-resistant strains of RSV;

D. A study of personnel caring for recipients (and/or those exposed in its manufacture), in which blood will be assayed for ribavirin during and after exposure to the aerosol;

E. Two oral (gavage) carcinogenicity studies (rat and mouse);

F. An inhalation study in rats that will provide for subchronic exposure with long-term follow-up for carcinogenicity (This study or a separate study should include an evaluation of toxicity in fetal or newborn animals including, but not limited to, assessment of effects of inhaled ribavirin on the developing lung and gonads.);

G. A study in animals to clarify drug disposition, retention and clearance as well as systemic exposure (blood and urine levels) following inhalation; and

H. A study or studies to define ribavirin's inhalation pharmacokinetics in the intended patient population.

VII. Approved Package insert

The approved package insert is attached.

Table I

Results of Studies of Ribavirin Aerosol in
Treatment of RSV Respiratory Tract Infections

| | | Study Day | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | -1 | 0[a] | 1 | 2 | 3 | 4 | 5 |
| Taber Study | | | | | | | | |
| Bronchiolitis score: | RBVN[b] | | 2.0(10)[c] | 1.5(11) | 1.0(9) | 0.6(7)* | | |
| | PLBO[b] | | 2.0(4) | 1.7(12) | 1.3(11) | 1.3(10)* | | |
| Viral culture[d]: | RBVN | | 3.0(10) | 1.9(8) | 0.9(4) | 0.9(4) | | |
| | PLBO | | 2.6(13) | 1.6(10) | 1.2(8) | 1.0(6) | | |
| Hall I Study | | | | | | | | |
| Illness score: | RBVN | 3.1(15) | 3.0(15) | 2.5(15) | 1.7(15) | 0.9(14)* | 1.0(5)* | |
| | PLBO | 2.8(15) | 2.4(17) | 2.3(17) | 2.2(17) | 2.1(13)* | 3.9(5)* | |
| Viral culture[d]: | RBVN | | 2.8(14) | 2.5(17) | 1.2(15) | 0.2(13)* | 0.2(5)* | |
| | PBLO | | 3.2(13) | 1.8(15) | 2.1(14) | 1.8(13)* | 1.6(6)* | |
| Hall II Study | | | | | | | | |
| Viral culture[d]: | RBVN | | 2.8(11) | 2.0(12) | 1.2(12) | 1.3(9) | 1.0(5)* | 0.2(5)* |
| | PLBO | | 2.5(8) | 2.0(10) | 2.4(10) | 2.3(8) | 2.9(8)* | 3.2(4)* |

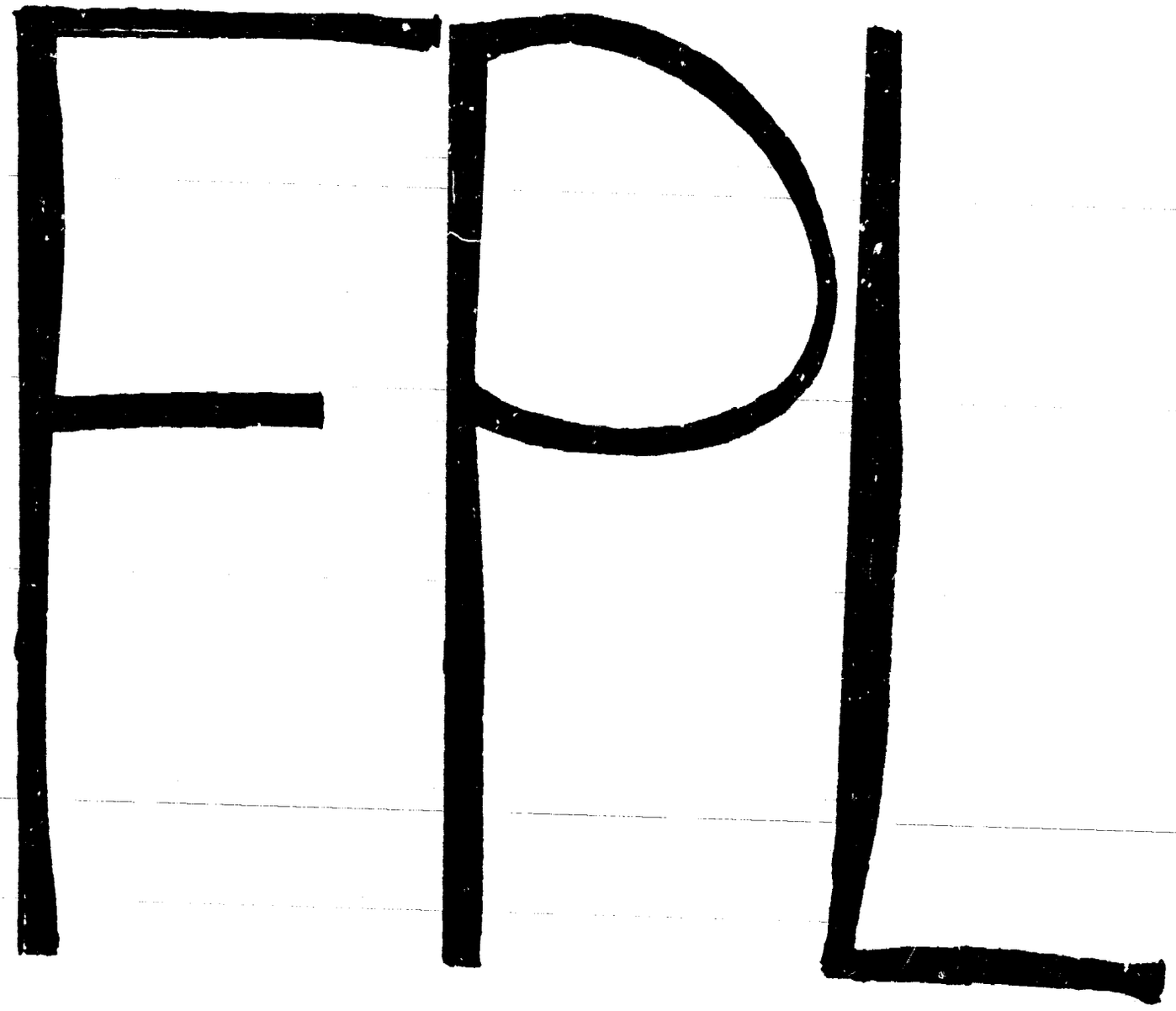
* - P less than 0.05, two-tailed testing
a - Ribavirin or placebo treatment started on day 0
b - RBVN = ribavirin; PLBO = placebo
c - Numbers in parentheses are number of patients
d - Log 10, half the tissue culture infectious doses per ml ($\log_{10}$ TCID50/ml)

Table 2

Average Symptom Score of Subjects Treated With Placebo versus Subjects treated with Ribavirin*

| | Average Score | | |
|---|---|---|---|
| | Placebo-Treated Group (N = 7) | Ribavirin-Treated Group (N = 6) | P** |
| Minor symptoms | 6.2 | 9.6 | NS |
| Systemic symptoms | 2.9 | 0.5 | .01 |
| Fever | 4.4 | 0.8 | .01 |

* - Hall et al. JAMA 1983; 249:2666
** - Wilcoxon's rank test


FPL

# Virazole™
## (Ribavirin)

Lyophilized Powder for Aerosolization

## PRESCRIBING INFORMATION

**WARNING:**

**RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.** Conditions for safe use with a ventilator are still in development.

Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

### DESCRIPTION:

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:

Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C, and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$, and the molecular weight is 244.2 Daltons.

### CLINICAL PHARMACOLOGY:

#### Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

#### Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

#### Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16µg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

#### Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 µM, with a mean concentration of 0.76 µM. The plasma half-life was reported to be 9 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 µM, with a mean concentration of 6.8 µM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

### INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

#### Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

### CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

### WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

### PRECAUTIONS:

#### General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

#### Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

#### Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

**Pregnancy:**

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

## ADVERSE REACTIONS:

Approximately 900 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilator's apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

## DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 mg wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

## HOW SUPPLIED:

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

## REFERENCES:


1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. *Antimicrob Agents Chemother* 17:770-775, 1980.
2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., RG. *In vivo* inhibition of respiratory syncytial virus by ribavirin. *Antimicrob Agents Chemother* 21:125-130, 1982.
3. Taber LH, Knight V, Gilbert BE, McClung HW et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory tract infection in infants. *Pediatrics* 72:613-618, 1983.
4. Hall CB, McBride JT, Walsh EE, Bell DM et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 308:1443-7, 1983.
5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. *J Clin Microbiol* 16:329-33, 1982.



**ICN Pharmaceuticals, Inc.**
ICN PLAZA
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
(714) 545-0100

MED
REV

NDA 18-859

November 14, 1983

# MEDICAL OFFICER'S REVIEW OF NDA 18-859

Date of submission: 9/21/82
Date of Receipt: 9/21/82
Date of Refusal to File: 11/2/82

Applicant: Viratek
222 North Vincent Avenue
Covina, California 91722

Name of Drug: USAN: Ribavirin
Trade: Virazole
Chemical: 1-B-D-ribofuranosyl-1,2,4-triazole-3-carboxamide

Category: Antiviral Classification: 2-C

Formulation: Aqueous aerosol, 20 mg/ml.

Proposed Indications: Treatment of Respiratory Syncytial Virus (RSV) infections.

Dosage and Route of Administration: Variable dosages administered by aerosol inhalation during variable periods of time from one to five days.

Related IND's:

Related NDA:

Manufacturing and Controls: Chemistry Review (#1) by William F. Kochert dated 1/9/83: "We have completed our review and find that the information presented is inadequate and the application is not approvable.

The application is inadequate under section 505(b)(4) of the Act as follows:

It fails to include a full description of the laboratory procedures that will be employed to check the specifications for the raw materials, water for injection USP.

It fails to submit stability data for the packaged drug product.

The application is also inadequate under section 505(b)(6) of the Act in that the type size of the name of the drug as it appears on the container label and carton is too small. See 21 CFR 201.10".

Pharmacology Review: By Norma J. Browder, Ph.D., dated July 29, 1983: "Recommendations:

A. In the BALB/3T3 in-vitro transformation assay, chemically-transformed cells were not transplanted into syngeneic hosts to establish if they were malignant and capable of forming tumors, as is required for the in-vivo part of this assay. A recommendation for the performance of both in-vitro neoplastic transformation studies and in-vivo tumor induction studies in syngeneic hosts was made to the sponsor in our letter of Dec. 6, 1976 and in a telecon held with the sponsor on 11/16/80 (refer to Dr. Browder's memo of this date).

B. The sponsor should again be requested to perform in-vivo tumor induction studies in syngeneic hosts using chemically transformed cells derived from the in-vitro portion of the BALB/3T3 transformation assay.

C. The positive results for mutagenicity obtained in the mouse lymphoma assay plus the results obtained with the BALB/3T3 transformation studies should be considered together with the results of the carcinogenicity studies in making an assessment as to the carcinogenic potential of ribavirin".

Clinical Pharmacology: Review by Jose G. Canchola, M.D. Very limited and inadequate clinical pharmacokinetics data on the aerosol formulation were submitted in the application. These data were reported by James Connor, University of California at San Diego . Each pediatric patients, age range 2 mos. to 17-years of age received aerosolized drug from 2.5 to 5.0 h/day for 3 days, either by mask or endotracheal tube. The investigator states that "the mean peak (plasma) level in the 6 patients analyzed to date is 1.3 uM". These data are clearly insufficient to evaluate the pharmacokinetics of the aerosol formulation. In addition, the technique utilized in this study, a RIA, appears to be unspecific for detecting ribavirin and metabolites, according to Vernon Knight, M.D, (meeting with sponsor held on 8/25/83).

The application also contains limited and inadequate data on the clinical pharmacokinetics of the oral and intravenous ribavirin formulation, as follows:

a. A publication by Catlin, DH, Smith RA and Samuels AI. $^{14}C$-ribavirin: distribution and pharmacokinetic studies in rats, baboons and man. In Ribavirin: A broad spectrum antiviral agent, p 83-93. Academic Press, Inc., 1980. In this study, three adult normal subjects received one single oral dose of $^{14}C$-ribavirin in aqueous solution. One subject received 3.1 mg/kg and the other two received 2.8 mg/kg. Peak plasma drug levels were detected between 1 and 1.5 hours with increased and sustained retention in RBC's and a t 1/2 of about 40 days. The urinary drug excretion at 72 hours was about 53% of the administered dose.

b. A report by Dr. A. Benakis, Faculty of Medicine, University of Geneva, Geneva, Switzerland, on the clinical pharmacokinetics of single oral doses of 300 mg $^{14}C$-ribavirin, given in a capsule from to five normal adult volunteers (4 females, one male).

Drug plasma levels showed a bi-exponential decrease with a mean t 1/2 $\alpha$ = 2.7 hours and mean t 1/2 $\beta$ = 42.7 hours. Extrapolation of urinary recovery levels, gave an estimated excretion of about 65% of the administered dose.

Clinical Studies

4. Controlled, single blind, randomized study of respiratory syncytial virus (RSV) infections in children. Performed by L. Taber, M.D., Baylor (1981-1982).

No case reports were submitted, only computer print-outs. Duration of RSV shedding was not provided.

Twelve infants received ribavirin aerosol and 14 placebo.

No significant difference between treatment groups of drug efficacy. The monitoring of drug toxicity was inadequate.

Conclusions: The study did not show evidence of drug efficacy.

5. Placebo controlled and randomized evaluation of ribavirin aerosol in induced RSV infection in young adult volunteers. Performed by Caroline B. Hall, M.D., University of Rochester Medical Center, Rochester, NY.

Eight volunteers received ribavirin aerosol or placebo (water mist), 12 h/day for 3 days, three days after intranasal RSV inoculation.

No data were provided on virus quantitation or duration of RSV shedding.

Monitoring of drug toxicity was inadequate. Hemograms and blood chemistry were done pre-dosing and at completion of dosing (day 3).

Conclusions: The study was not adequate to evaluate potential drug toxicity.

6. Placebo controlled, double blind and randomized evaluation of aerosol ribavirin in RSV infection in children. Performed by Caroline B. Hall, M.D., Rochester, NY (1982).

Sixteen infants with a clinical diagnosis of bronchiolitis were entered into the study. Eight received ribavirin aerosol and 8 placebo (water mist) in a tent.

It is stated that treatments were given, on the average, 18 hours/day for 4 to 5 days. However, length of inhalation, frequency of inhalation per day and duration of treatment, was not recorded for 5 of 8 drug-treated and for 2 of 3 placebo-treated infants.

Data on RSV titrations and duration of viral shedding were not provided.

One infant in the drug group had croup with negative RSV isolation. Of the remaining 7 infants, 4 had a diagnosis of bronchiolitis, 2 pneumonia, and one had no specified diagnosis. This last patient developed paroxysmal atrial tachycardia on the 3rd-day of treatment; another patient with pneumonia had a relapse two days after completion of treatment.

Among the 8 placebo infants, 2 had bronchiolitis, 1 pneumonia, 2 croup, one apnea, one diarrhea, and one a vascular ring. Except for one patient where the code was broken and he was then put on ribavirin aerosol, it is unclear how many other placebo-treated patients were crossed over to drug treatment.

There were no hematological data during or after treatment provided, nor data on follow-up pulmonary function tests.

Conclusions: This placebo controlled study was not adequate for evaluation of drug efficacy or safety.

Recommendations: As it has been already decided, the application is incomplete, and it should not be filed because of the following reasons:

1. Manufacturing and controls for the aerosol formulation are not satisfactory.

2. Lack of preclinical animal toxicity data.

3. Inadequate data from controlled clinical studies of the aerosol formulation in RSV respiratory tract infections for evaluation of drug safety and efficacy.

4. Inadequate and incomplete clinical pharmacokinetics data on the aerosol formulation administered by mask, tent or endotracheal tube.

NDA Amendment (dated October 27, 1983) (received on November 3, 1983; assigned on November 14, 1983). The sponsor states that it "submits this new drug application... The application supports the safe and effective use of Virazole (ribavirin) given in small particle aerosol for the treatment of hospitalized infants with respiratory syncytial virus infections"...

"This application is a replacement for NDA 18-859 which we are hereby withdrawing..."

"The (initial) submission represented by NDA 18-859 included claims for . these claims are not contained in the enclosed submission..."

"We deem it appropriate to request a meeting with you and your reviewing staff to present the new data...for small particle aerosol for treatment of respiratory syncytial virsus in children... We have enclosed an agenda for this meeting".

## Review

1. Placebo controlled, double blind and randomized clinical study of aerosol ribavirin in RSV infection in children. Caroline B. Hall, M.D. Rochester, NY (Winter 1982-1983).

It is stated that "Infants enrolled in the study were admitted to the infant ward or pediatric intensive care unit with lower respiratory tract infection proved to be caused by RSV by immunofluorescent antibody testing and subsequently by viral isolation. Sixteen infants were admitted during January-March, 1982 and an additional seventeen during January-April, 1983. Only those infants wh were deemed ill enough to require at least three days of hospitalization were considered. Infants with underlying diseases such as

"Infants were assigned by use of a random table in a double-blind manner to receive either drug or placebo (water)...The aerosol was administered...at a rate of 12.5 liters per minute into an infant oxygen hood, oxygen tent or inhalation tubing of a respirator... The exact dosage of ribavirin delivered to an infant cannot be determined as small particle disposition in infants has not been measured."

"Assays to detect presence of ribavirin in nasal washes. .. rder to be sure that ribavirin was not still present in the secretions interfering with viral growth, specimens from four patients were tested in the same system used for viral titration. Nasal wash specimen were heated at 65°C for 30 minutes to inactivate any virus present. To these specimens $10^3$ $TCID_{50}$ of RSV (Long strain) was added and titrations were performed... The titers of these samples were comparable to the control titrations...".

"Thirty-three infants with proven RSV lower respiratory tract disease were studied. All these infants had RSV pneumonia, confirmed by chest roentgenograms, with or without bronchiolits. Seventeen patients were randomized to receive placebo and 16 received ribavirin".

"Aerosol treatment was administered...for an average of 20 hours per day for 3-6 days with an average of 4.9 days in the ribavirin group and 4.7 days in the placebo group. On admission, the severity of illness of the infants in the placebo group was not significantly different from that of the infants in the ribavirin group... However, by the time therapy was initiated (an average of 1.5 days from admission), the infants in the placebo group had improved, such that their illness score was significantly less than that of the ribavirin group...the subsequent improvement after the first day of therapy was greater in the group treated with ribavirin, and their illness severity score by the fourth day of therapy was significantly less."

"The change or degree of improvement in the lower respiratory tract signs, except for wheezing, was significantly greater in the ribavirin-treated group, whereas the change in temperature and upper respiratory tract signs was not significantly different between the two groups".

"The initial means $SaO_2$ or $PaO_2$...of the two groups were not significantly different... By the the end of therapy, the ribavirin treated infants demonstrated significant improvement... The improvement in the placebo group was significant but less..."

"By the end of treatment...the quantity of virus in the nasal washes of the ribavirin group was significantly less...".

"Two infants who had ceased shedding RSV at the end of treatment with ribavirin, 3 and 4 days later had a nasal wash specimen that showed the presence of RSV... In one of these infants, the positive nasal wash was associated with clinical relapse..."

"No toxicity or side effects from the aerosol therapy were noted in any infant. Complete blood cell counts obtained before, during and the end of therapy were not significantly different between the placebo and ribavirin groups, and no hematologic abnormality was noted... All of the 16 infants hospitalized during 1982 have had follow-up examinations 3-9 months after discharge. The $SaO_2$ determinations...did not differ significantly between...drug versus placebo."

Reviewer's Conclusions:

The second "randomized, placebo controlled and double blind study of RSV infections in children, performed by C. Hall, M.D., contains important flaws and her analyses of drug safety and efficacy are biased.

According to the protocol design, the study was randomized and placebo controlled (water mist). In addition, infants with underlying diseases such as congenital heart diseases were to be excluded. It appears that the study was not randomized nor placebo controlled.

Seventeen infants were entered into the study. Eight received ribavirin aerosol from 14 to 102 hours, and 9 received no treatment. Of the 8 ribavirin-treated infants 2 had RSV pneumonia, 2 bronchiolitis, 1 bronchiolitis and pneumonia, 1 reactive airway disease, 1 asthma and otitis, and 1 had no diagnosis established. Half of the patients received broncodilators along with ribavirin treatment.

Of 9 control untreated patients (no placebo given), 4 had broncholitis, 1 croup, (negative RSV), 1 S. pneumoniae pneumonia, 1 pneumonia, and 2 no bronchiolitis or pneumonia. Three patients had congenital heart disease (2 coarctation of the aorta, 1 VATER syndrome) and one patient had congenital pulmonary dysplasia and hydrocephalus. Thus, 4 (44%) of the 9 control patients should have been excluded from the study because of underlying congenital heart disease or pulmonary disease.

It is very unlikely that the study was randomized with no patients with congenital heart or lung disease allocated into the drug-treated group.

Only one controlled patient (croup, RSV negative) received bronchodilators (vaponephrine).

At entry, all ribavirin-treated patients had positive RSV isolation whereas only 7 control patients were RSV positive. No titers or duration of RSV shedding was provided.

Baseline $SaO_2$ were not recorded or done for 2 ribavirin and 6 controlled patients. Blood chemistries were not done. CBC's were done mostly at entry, and in some cases were not done at all.

At least two control patients with bronchiolitis were switched to ribavirin aerosol (one from day 1 of the study, and the other one from the day 4 of the study).

These are not data available on short or long-term follow-up observations.

Therefore, this additional study is not adequate to confirm or support the efficacy and safety of ribavirin aerosol in RSV broncholitis or pneumonia in children.

2. Publication: Hall CB, McBride JT, Walsh DE, Bell DM, Gala CL, Hildreth S et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. A randomized double blind study. New Engl J Med 1983; 308: 1443-1447.

Critique: The clinical investigator, Caroline B. Hall, M.D., pooled the data from the two limited clinical studies already discussed by this reviewer. The data from these two studies are not poolable:

a) The control group received water mist in the first study, and no treatment in the second study; thus, evaluation of treatment effect(s), drug vs placebo in the two studies, was not comparable: b) the control groups in the second study had only 3 bronchiolits cases with confirmed RSV isolations; c) it is not known how many patients in each study received the drug by aerosol into an oxygen hood, oxygen tent or inhalation tubing of a respirator.

In addition, quantitation and duration of RSV shedding were not provided and monitoring of drug biochemical toxicity was deficient.

Therefore, the conclusion of drug safety and efficacy reached by the clinical investigator are not supported by the data provided in the case reports.

3. Double blind, placebo controlled study of ribavirin aerosol in RSV infections in children. L. Taber, M.D., Baylor, 1982-1983.

Seven infants were randomly treated with drug aerosol (2-5 days) and 7 with distilled water aerosol (2-4 days). RSV bronchiolitis was confirmed in all infants, except in one drug-treated patient.

No case reports were provided and the computer point-outs were incomplete. The evaluation of biochemical toxicity was inadequate.

The investigator concluded that "there was no difference in the two groups of patients... Illness was never severe in these patients.. Statistical significance with this mild illness and low number of participants is hard to demonstrate".

"Virus shedding...was not significantly different in the two groups..."

"The hematological studies show no evidence of ribavirin toxicity".

Conclusion: This second study did not support efficacy, and it was inadequate for evaluation of drug toxicity.

In spite of its limitation, the study does not support the drug efficacy claimed by Dr. Hall.

4. Controlled, double blind and randomized clinical study of ribavirin aerosol in RSV infections in children. Kenneth McIntosh, M.D., Children's Hospital, Harvard, Jan.-March, 1983.

Eleven infants with a clinical diagnosis of bronchiolitis were enrolled in the study. Five infants received ribavirin and 6 received no treatment. Ribavirin aerosol was given, on the average, 16 hours daily for 3 days (non-ventilated) or 18 hours daily for 5 days (ventilated). Control patients received no placebo aerosol. There were 3 ribavirin and 4 control patients who did not require assisted ventilation, and 2 patients in each group who were intubated and ventilated.

RSV was isolated from 4 ribavirin and 5 untreated control patients. In some patients CBC's and blood chemistries were done at the start of the study and at the completion of treatment.

The investigator stated that "At this point, a number of considerations can be be made concerning the drug's delivery via a ventilator... Infants were ventilated with a Health-Dyne time-cycle pressure limited venitilator. The drying chamber outlet of the aerosol unit was connected to the heated expiratory limb of the venitlator and the aerosolized drug had to pass through a humidifier before reaching the infant. An enormous amount of fluid was noted 'to rain-out' in the tubing prior to reaching the patient. Furthermore, the pressure wave delivered to the infant was significantly altered by using flow through the nebulizing apparatus alone to deliver breaths to the infant. Such an alteration can significantly change the distribution of ventilation and ultimate gas exchange. Close scrutinity on the drug group patients reveals a suggestion of improved gas exchange during rest periods off the nebulizing equipment or shortly thereafter, while under aerosolization alone".

The investigator concluded that "no conclusions are possible from these very small patient samples. The suggested evidence of efficacy of ribavirin aerosol has no statistical significance, however, the clinical tolerance to the drug was excellent without any laboratory evidence of drug related toxicity".

"The administration of ribavirin aerosol through a ventilator requires close scutinity. The necessity for humidifying air delivered directly to the trachea of a patient may alter drug distribution and delivery. The resulting aerosolyzed drug-particle may be too large to be able to reach deep into the lung, the areas which are infected".

"Further evaluation and study of this problem is needed".

Conclusions: This limited study was not adequate to evaluate drug efficacy and it was deficient to document drug toxicity. In spite of this, the review of the case reports did show that duration of hospitalization and RSV shedding were prolonged in the ribavirin group; these facts are in contradiction with Dr. Hall's results.

5. Compassionate clinical use of ribavirin aerosol. Sixteen children and 2 adult patients were treated. Of the 16 children treated, 7 had severe combined immunodeficiency, 1 Down's syndrome, and 1 acute lymphocytic leukemia. RSV pneumonia was documented in 5, parainfluenza (type 3) pneumonia in 1, adenovirus pneumonia in 2, and ECHO (type 11) pneumonia in 1.

RSV either was not inhibited or became reactivated after treatment in 4 of 5 RSV-pneumonia patients; parainfluenza also became reactivated after treatment, and ECHO 11 was not inhibited. The 2 patients with adenovirus infection died very early after initiation of treatment.

These results are strongly suggestive of lack of activity of aerosol ribavirin in RSV infections of the lower respiratory tract.

The drug inhibitory results reported by Dr. Hall may be due to drug carry-over in the clinical specimens collected for RSV isolations. She has claimed that this is not the case, because she has heated (65°C for 30 minutes) the clinical specimen to inactivate RSV, and then she has added an inoculum of RSV to the heated specimens. She has stated that simultaneous titrations of the heated and original specimens have yielded similar RSV titers. However, she failed to evaluate the stability of ribavirin when heated at 65°C for 30 minutes. The proper way to do these evaluations is to neutralize ribavirin in the clinical specimen with an adequate quantity of either guanosine or xanthosine.

6. Clinical pharmacokinetics. The clinical pharmacokinetics data are deficient and incomplete. These data are included in a copy of a presentation by James Connor, M.D., using a RIA, at the recent second symposium on ribavirin. The data presented by Dr. Connor totally ignore the determination of the retention time of ribavirin in erythrocytes.

In addition, the specifity of the RIA has been seriously questioned by Vernon Knight, M.D., at a meeting held with the sponsor on August 25, 1983.

General Conclusion: NDA 18-859 still remains incomplete, regarding the requirement for substantial evidence on the safety and efficacy of aerosol ribavirin in the treatment of respiratory tract syncytial virus infections in children, and children and adults.

Recommendations:

1. NDA 18-859 should not be filed and the sponsor should be informed in writing about all the reasons for refusing to file the application and the amendment.

2. The meeting requested by the sponsor to discuss the recent NDA amendment should not be granted at this time, until an internal decision to have a pre-NDA meeting is reached in the future.

3. The sponsor should be requested to provide promptly all the available data to demonstrate that the RIA being used in clinical pharmacokinetics studies is specific, sensitive and reproducible.

4. The sponsor should be requested to submit for review and recommendations, a newly well designed protocol for controlled clinical studies of the aerosol formulation in the treatment of lower respiratory tract RSV infections in children.

5. HFN-140 should give serious consideration to imposing a clinical hold on the clinical studies being performed with the aerosol formulation, until the time the sponsor submits adequate preclinical animal toxicity data for the aerosol formulation, and documented evidence on the availability of an adequate technique for the performance of clinical pharmacokinetics studies.

6. HFN-140 should also seriously consider the submission of a letter to the Editor, N Engl J Med, with a fair critique of the findings recently reported by Dr. C. Hall at al, on the safety and efficacy of ribavirin aerosol in RSV infections in children (Hall CB et al N Engl J Med 1983; 308: 1443-1447).

Jose G Canchola

Jose G. Canchola, M.D., M.P.H.

cc:
ORIG. NDA 18-859
HFN-140
HFN-140/JGCanchola/sdj/11/29/83
HFN-140/CSO/JCurtis
HFN-220
0864a

# Medical Officer's Review #1

| | | |
|---|---|---|
| NDA 18-859 | | |
| Amendment 6 | Submitted: | 6-24-84 |
| Amendment 7 | Submitted: | 6-29-84 |
| Amendment 8 | Submitted: | 6-29-84 |
| Amendment 9 | Submitted: | 7-3-84 |
| Amendment 10 | Submitted: | 7-13-84 |
| Amendment 15 | Submitted: | 9-14-84 |
| Amendment 17 | Submitted: | 9-20-84 |

Received by Reviewer: August-September, 1984

Completed: 10-16-84

Applicant: Viratek
222 North Vincent Avenue
Covina, California 91722

Name of Drug: USAN: Ribavirin
Trade: Virazole
Chemical: 1-B-D-ribofuranosyl-1,2,4-triazole-3-carboxamide

Formulation: Aqueous aerosol, 20 mg/ml

Proposed Indications: Lower respiratory tract respiratory syncytial virus infection.

Dosage and Route of Administration: Aerosol inhalation for variable time periods.

Related IND's:

Related NDA:

Manufacturing and Controls: Chemistry review by Dr. Taylor complete, but not available to reviewer. Apparently, numerous deficiencies have been noted.

Pharmacology Review: Dr. Browder, Amendment dated 2-18-84, review of 4-17-84.

No information on pharmacodynamics or pharmacokinetics are included in this review. No human data are included in Amendments presently being reviewed. Toxicology showed:

"Rats exposed to ribavirin aerosol by inhalation for 12 hr/day, 7 days/week for 28 days via whole body chambers, receiving inhaled doses of 22, 36 and 57 mg/kg showed: mortality at all dose levels occurring as early as day 6 and gasping followed by convulsions prior to death at 57 mg/kg".

"Microscopically, lesions of the following organs were observed in drug-treated animals: lungs (alveolar edema and hemorrhage as well as hypertrophy and hyperplasia of intrinsic alveolar cells (adematosis) and foam cell (pulmonary macrophages) accumulation in alveoli); heart (inflammation of the pericardium and myocardium, frequently associated with myofiber necrosis and interstitial edema); thymus (atrophy, characterized by necrosis and loss of cortical cells at 36 and 57 mg/kg); liver (focal or multifocal infiltration at 22, 36 and 57 mg/kg)."

"Mice exposed to ribavirin aerosol by inhalation for 12 hrs/day for 7 days/week for 28 days using whole body chambers and receiving inhaled doses of 30,62 and 111 mg/kg showed: mortality at all dose levels, occurring as early as day 7; high incidences of irregular breathing in all drug-treated groups. Microscopically, lesions of the following organs were observed in drug-treated animals:

-Thymus (atrophy characterized by necrosis and a reduction of cortical tissue at 111 mg/kg).

-Bone marrow (hypocellular at 111 mg/kg); large intestine (enteropathy at 111 mg/kg characterized by "loss or crypts, occasional epithelial giant cell formation and slight infiltration of lamina propria by macrophages).

"The sponsor submitted the above inhalation toxicity studies in support of their IND and NDA for the aerosol formulation of Virazole. With respect to these studies, Viratek indicates that they regard the results to be inaccurate and misleading."

"In addition, as a result of a GLP/Data Audit inspection of these studies conducted on 8/23-9/6/83 by FDA, Chicago District, this Division (HFN-815) was notified that the final report of the completed studies submitted by Viratek to FDA was unsigned by personnel involved in the study, thus constituting a violation of GLP."

Results from aerosol studies in developing ferrets have been reported incompletely to Dr. Browder, who awaits completion of that study before it can be reviewed.

Clinical Background: Reviewed in Medical Officer's Review of 11-14-83.

Clinical Studies:

1. Ribavirin treatment of respiratory viral infections in infants with underlying disease. Performed by Dr. Caroline Hall, University of Rochester, Rochester, New York.

Amendments (7 and 15)

No protocol was submitted to reviewer, although one was requested from sponsor. The data summary submitted by the sponsor June 29, 1984 contained numerous discrepancies when compared to the case report forms prepared by the investigator. The sponsor assured me that all discrepancies were due to investigator error. However, the investigator indicated to me that the sponsor was notified in June, 1984 that the summary tables were incorrect. The following review is based on a report and summary provided by the investigator to the sponsor, NDA-amendment (15)

During winter 1983-84, the efficacy of ribavirin in treatment of RSV lower respiratory tract disease was studied. RSV infection was documented by isolation of virus or detection of RSV antigen in nasal wash specimens and nasal swabs respectively.

The patients, all 1 yr age, were randomized. A compassionate use protocol was in effect in the same institution at the same time, and it is not stated how infants were chosen for randomization versus compassionate use.

Subjects received drug or placebo continuously except when nasal wash was obtained (1-3h) or during other procedures requiring removal of infant from aerosol. Actual times of drug administration are not given. The rate was 12.5 L/min. The ribavirin concentration in the liquid reservior was 20 mg/ml. The mode of administration was into an infant $O_2$ hood, $O_2$ tent, or inhalation tubing of respirator. However, the mode that was used for each subject is not given.

Clinical evaluations were performed by a blinded investigator. Severity of illness was evaluated on a visual analog scale ( 0 = normal; 10 + = most severe).

No safety data are summarized. No criteria were given for removing a patient from the study.

There were 12 ribavirin recipients and 10 placebo recipients in whom RSV infection was documented. The groups were similar in distribution of infants by age, sex, prematurity and underlying cardiovascular disease. The groups were possibly different at the outset with respect to illness severity (Ribavirin 6.1, placebo 4.5, p = .067). However, this difference is not statistically significant and may have occurred because of the relatively small number of subjects studied or a flaw in the randomization procedure. There was no difference in illness severity at the end of therapy (ribavirin 3.0, placebo 3.3, p = .7). The incremental improvement in score was significantly greater for ribavirin than for placebo

recipients (3.0 vs 1.2, p = .007). The incremental improvement may reflect ribavirin efficacy. However, if ribavirin were effective and the comparison groups were similar, a difference in scores should have been evident at end of therapy. Alternatively, if the ribavirin group were sicker at start of therapy, the superior incremental improvement may have resulted from the natural history of more severe disease and not from ribavirin effect.

The summarized analog scores still cannot be verified on all case report forms. The clinical validity of the subjective analog score is unknown.

Arterial $O_2$ saturation ($SaO_2$) was not different either at start or at end of therapy between the two groups. Therefore, the clinical relevance of the statistically significant incremental change is unknown and may not reflect ribavirin efficacy.

Data were collected for many other clinical parameters which might form suitable efficacy end-points, including vital signs, behavioral and feeding parameters, chest physical findings, $FiO_2$, blood gases and chest x-ray. Analysis of these data has not been submitted.

Viral titers were significantly less in the ribavirin recipients compared to the placebo recipients studied on days 5 and 6 of the study. Thus, ribavirin demonstrated anti-viral efficacy.

Conclusions: The data analysis from this study does not conclusively support a claim for ribavirin efficacy based on meaningful clinical endpoints. The drug, however, showed antiviral efficacy on d5 and d6. No conclusion as to safety can be made without an analysis of the safety data.

2. Randomized, single-blind, placebo-controlled study of Ribavirin in RSV infection. Drs. Parrott and Rodriequez, Children's Hospital National Medical Center, Washington, D.C.

Amendments (9 and 17)

The original data submission consisted of the investigator's computer data printout and a summary provided by the sponsor. It was impossible to verify any data. In response to a request for uncoded, raw data and a summary of that data, Amendment 17 ( 700 pages) was submitted. This review is based on Amendment 17.

The data are still not provided in a format to allow ready verification of the data. However, this format change may not be necessary since no clinically significant and only one statistically significant end-point of efficacy are mentioned in the investigator's report. The sponsor's conclusion that the drug is safe might be verified with the requested change in format.

The purpose of the study was to show efficacy of ribavirin as compared to placebo in respiratory syncytial virus infection.

The study is described as single-blind. It is irrelevant that the infants did not know if they were receiving drug or placebo. However, knowledge of treatment by the investigator compromises any conclusions which might be drawn from the data. Other studies presented by the sponsor are said to be double-blind. Why wasn't this one double-blind if a placebo was included?

The method of aerosol administration is not specified. (Tent vs. hood vs. respirator).

It is not clear if, when, or why any patients had to be removed from the study.

The following is based on the investigator's report since data verification was not feasible from the NDA submission or Amendment (1). Subjects received ribavirin (9 females + 11 males) or placebo (8 females + 2 males). Average age for the placebo group was 3.2 mo vs. 6.1 mo for the ribavirin group. The groups are too small for the apparent age or sex differences of biologic importance to be statistically significant. The groups were similar with respect to neonatal history, past medical history, extent of RSV pneumonia, duration of illness prior to treatment, or prior to admission, and duration of treatment. It is not specified what exclusions took place. Was a compassionate use protocol in effect at the same time? Were all RSV infections randomized?

The safety claim by the investigator/sponsor cannot be verified due to data format. In addition, no information is provided as to how ribavirin affected ventilator settings or blood gases in patients requiring respirator.

There was no efficacy observed as judged by duration of fever, respiratory rate, chest physical findings, irritability, lethargy, food intake, oximetry, or illness score. Although statistically significant temperature differences in favor of ribavirin were seen, the differences are of minor or no clinical importance.

There appears to be a deliberate attempt on the part of the sponsor to imply that significant differences in illness score were observed. However, significant p values refer to published work of another investigator. The method of determining the illness score is not given. A subjective illness score is virtually meaningless with an unblinded investigator.

There was no demonstration of antiviral activity.

The small sample size with the 2:1 randomization would make it hard to show efficacy even if it is present.

Conclusion: Efficacy is not shown. Safety data have been collected and summarized but cannot be verified in present format.

3. Respiratory Syncytial Virus Infection in Children. Kenneth McIntosh, M.D., Children's Hospital, Boston, Massachusetts.

Amendment (6)

No protocol was submitted to reviewer, although one was requested from sponsor. No investigator's report was submitted.

The sponsor characterizes the study as blinded, but controls apparently received no treatment. The study is said to have been randomized, but no information is given as to how this was to be accomplished. No inclusion or exclusion criteria are given.

The drug is said to have been administered 12-18 h daily for 3-5 days, but no daily record of aerosol treatment is found in the investigator's case report form. The concentration of drug in the reservoir of the Coleson generator was 20 mg/ml. The mode of administration (tent, hood, respirator) is not specified. The case report form has an undefined variable of possible interest -- "non-vent hours."

Patients were evaluated by "clinical scoring", the sum of 0-3 points assigned subjectively for general activity, 0-4 points for respiratory rate, 0-4 points for heart rate, 0-3 points each for cough, retractions, lower airway, and 0-2 points for grunting. Only the total score (an artificial parameter) data were analyzed. Additional parameters were: feeding volumes, $S_aO_2$ temperature, duration illness (preadmission, total), CBC, chemistries, UA, chest x-ray, and viral studies. However, data are missing or not analyzed for many of these parameters.

Data verification was not possible for many variables. The summarized data were not internally consistent. For example, Table II Hospitalization (hours) disagrees with Table IV Hospitalization (hours) for every entry. Moreover times of hospital admission and discharge are not given on the case report form so neither value can be verified. There are similar problems for study (hours), Table IV. No virology data is provided on the 1983-1984 case report forms. Many case report forms are missing data on illness onset. The illness termination is apparently assumed to be the date of hospital discharge. This assumption is not justified. Gestation in weeks is not given on most case report forms. Apparently, infants designated at FT (full-term) have all been assigned a value of 38 weeks, which invalidates the statistical analysis in Table III. Treatment (hours) Table II is not defined. If this parameter is recorded on the case report forms as "non-vent" hours, there are many discrepancies between the summary and the case report forms. Tables VI, VII, VIII refer to parameters (feeding $O_2$, illness score) at entry and discharge, but it is not specified entry/discharge to hospital or to study. There is inconsistency in how the data are summarized. Some represent hospital entry vs study discharge, etc.

Feeding volumes are averaged in Table VI even though the data are not normally distributed. It is not appropriate to average NPO volumes of zero with other values.

Many case report forms are not readable. Not all data have been recorded. Often, the study day (or date) for the data sheet is missing. No toxicity data are given or summarized.

Even if the above problems are set aside, the summarized differences in favor of ribavirin are of negligible or unknown clinical importance. Although the clinical score averaged 1.7 points (of total possible 22 points) lower in the treated patients, this difference could be due to a difference in pulse of 1 beat/min and a difference in respiration of 1 breath/min.

Antiviral activity is suggested by the ELISA studies for RSV antigen. However, this was not confirmed by quantitative viral cultures, and may be of no clinical significance.

Conclusion: The lack of a placebo, a protocol, verifiable efficacy data, and any safety data, make it hard to judge this study. The evidence for clinical efficacy -- a 1.7 point advantage on a 22 point artificial, partially subjective scale -- is miniscule and not based on a meaningful clinical endpoint. The evidence for antiviral activity is based only on a measure of RSV antigen and not on infectious virus.

4. Respiratory Syncytial Virus Infection in Children. Dr. Larry Taber. 1983-1984; Texas Children's Hospital and Ben Taub General Hospital. Houston, Texas.

Amendment 8

This study was not evaluated for efficacy. The computerized data are not presented in a readily verifiable format. Only 9 of 20 subjects had documented RSV infection. The sponsor characterizes the study as "randomized with a control group" which is consistent with the protocol indicating no use of placebo; yet the sponsor claims that the clinical course was assessed in a "double-blind study". This very unusual claim suggests that the pediatricians in the investigator's hospital would not recognize the small particle generator, an unlikely scenario.

The sponsor say general evaluation, $F_iO_2$, $p^{O}2$, $O_2$ saturation, and ventilator rates showed "lack of toxicity due to ribavirin aerosol." However, no data analysis is shown.

Virologic data are not summarized. However, according to the sponsor, "quantification of virus was erratic".

The summarized hematology data cannot be readily verified. There is a suggestion of increased eosinophil count with ribavirin use, but this was not analyzed statistically.

Conclusion: This study, as presented, cannot be used to support claims for efficacy or safety.

5. Respiratory Syncytial Virus Infection in Children. 1983-1984. Paul Edelson, R. Gordon Douglas, et al., Cornell Medical Center, New York, N.Y.

Amendment(10)

The protocol calls for a double-blind study with use of placebo when aerosal machine available. Patients were to be randomized. However, the protocol did not call for division into high and low risk groups as was performed. According to the sponsor, the high risk group included patients with pre-existing pulmonary, cardiac, or immunologic disease. However, not all "high risk" patients fit these criteria. Treatment was expected to be of 3-4 days duration; however, the protocol lasted longer than this in some cases. Two patients were enrolled and apparently used in the analysis twice. Two patients were "unblinded" and apparently used in the analysis anyway.

Editing of data is poor where it can be judged. However, most of the summarized data are presented in a format where they cannot readily be checked against the case report forms.

No statistical analysis has been shown. No claim of significance is made for differences of interest between ribavirin and control groups.

No RSV-IgE data are shown except in summary. Data showing differences with 10% confidence levels are generally not considered significantly different in medical research. The sponsor's conclusions that ribavirin could prevent immunologically mediated RSV disease are not justified by the data shown.

No information is provided as to the actual mechanism or duration of drug delivery. It is not possible to verify from the case report forms study numbers, mode of treatment, or whether or not placebo was used in controls. Drug absorption was to be measured, but no data are given.

Safety data have not been recorded regarding the drug delivery system. Other toxicity data have not been analyzed or summarized.

Conclusion: The data may be useable. However, the summarized data are not accurate in the few instances where verification from case report forms is possible. No statistical analysis has been shown. The data as presented cannot be used to support claims of efficacy or safety.

Conclusions Regarding Clinical Trial Data Submissions (1-5 above): These 5 studies of RSV infection differ as to inclusion/exclusion criteria, diagnostic and virologic methodology, study design, clinical observations, endpoints of safety and efficacy, and data collection, analysis and presentation. Detailed protocols outlining the study plan were available to the reviewer for only 3 of the studies. These protocols often differed importantly from the reported studies. In all 5 studies, the sponsor's data summary could not be verified either because it disagreed with the investigators' data or, more often,

because it was not possible to identify the source of the summarized data from the investigators' records. In no study was a complete data analysis presented. In no study was it possible to judge how long patients actually received the drug, how the drug was administered, whether or not difficulties in administration were encountered, how the drug concentration reaching the patient was influenced by use of hood vs. tent vs. respirator, how the drug affected respirator settings, or how much drug was absorbed by the patient. In several studies the sponsor claims a "blind" design where only the baby could not have known whether or not he was a control. No study reported how chest x-rays were influenced by use of drug although most patients hospitalized with RSV infection have chest x-ray examinations and many have infiltrates. Only $SaO_2$ data were analyzed although most hospitalized patients with serious respiratory tract disease have sequential determinations of $pO_2$, $pCO_2$, and pH. No study addressed the well known problems of aerosol administration in babies -- fluid overload, hyponatremia, collection of aerosolized material in GI tract instead of respiratory tract. No study addressed the known or theoretical toxicities of ribavirin.

No study conclusively demonstrated clinical efficacy. The strongest suggestion of efficacy was the superior incremental improvement in clinical score noted in Dr. Hall's data. However, placebo and treatment groups were equivalent at end of treatment. The statistically significant temperature differences reported by Dr. Rodriequez are of no clinical importance. Dr. McIntosh's 1.7 point ribavirin advantage on a 22 point artificial, partially subjective scale is not a meaningful clinical endpoint. No efficacy claim is made for Dr. Tabers' data. No statistical analysis has been presented to support the sponsor's claims about Dr. Edelson's study.

Virologic efficacy has probably been demonstrated by Dr. Hall and possibly by Dr. McIntosh. However, the important adjunctive microbiologic data does not constitute a demonstration of clinical efficacy.

No study presented data to support a claim of safety.

Statistical Review: Mr. Gebert noted many of the same deficiencies as this reviewer. A pertinent exerpt from his report follows:

> Overall Comments: The five studies in this submission have shown only weak evidence of efficacy for ribavirin. Results seen in one study were not corroborated in other studies. Except for some weak evidence that ribavirin reduces RSV more than placebo as measured by the titers from the nasal washes, the sponsor has not demonstrated sufficient evidence to show that ribavirin is more effective than placebo in reducing any disease symptom or objective measure that reflects the patients disease state.
>
> These studies would have difficulty showing the efficacy of ribavirin even if it was effective because the sponsor has failed to standardize the studies, he has failed to analyze objective measures of efficacy and, except for oxygen saturation, he has failed to analyze the same efficacy available in more than one study. He has also been negligent in his data editing and summarizations. In fact, the investigators have had to provide the correct analyses to compensate for the poor work of the sponsor.

The weak evidence of efficacy can be summarized as follows:

1. The log titer data of Dr. Hall and the corrected O.D. data, the appropriateness of which is unknown, of Dr. McIntosh favor ribavirin over placebo.
2. A very artificial variable (clinical score), which is the sum of 7 symptom scores, favored ribavirin in the McIntosh study.
3. The analysis of the presence of rales at day 5 only in the Parrott study favored ribavirin.
4. Improvement in oxygen saturation in the Hall study favored ribavirin.
5. A highly questionable analysis of improvement scores for illness severity in the Hall study favored ribavirin.

Against this weak evidence are the facts that all patients improved and were usually discharged after three to five days, irrespective of treatment; there was no difference between treatment groups at the end of the trial in the Hall study; and the log titer values from days 1 and 3 showed no difference between groups in the Parrott study.

General Conclusion: Neither safety nor efficacy have been demonstrated for aerosol ribavirin for RSV infection.

Recommendations: Before the NDA is approvable, numerous deficiencies will have to be corrected as outlined in chemistry and pharmacology review. In addition, clinical data summaries showing statistically significant advantages for ribavirin as compared to control subjects for meaningful clinical end-points are required for at least two studies. These summaries must be accompanied by the investigators' data used to generate the summary. It is necessary that the summarized data be readily identifiable for verification in the investigator data. There should be few discrepancies between the two data presentations.

Victoria Schauf

Victoria Schauf, M.D.

cc: Orig. NDA
HFN-815 ET 12/24/84
HFN-815/CSO
HFN-220
HFN-815/VSchauf:th/10/18/84
1944b

NDA 22Oct84

Medical Officer's Review (#2)
Amendments No. 19, 22, and 24, and 25 to NDA 18-859

Received by Reviewer: 11/26/84
Completed by Reviewer: 12/11/84

Applicant: Viratek
222 North Vincent Avenue
Covina, CA 97122

Name of Drug: Ribavirin

Clinical Studies:

Hall - Study I: This submission is a copy of the one previously reviewed by Drs. Canchola and Gebert. I agree with their reviews that clinical efficacy cannot be verified from the data. I will advise sponsor to: 1) provide original data showing placebo was used; 2) explain how 4 point illness scale data for 1982 were merged with 10 point scale data for 1983; 3) explain which underlying diseases were excluded and which were allowed; 4) provide a new summary excluding patients with underlying cardiopulmonary disease, e.g. control patients and and excluding patients without documented RSV infection, e.g. patient ; 4) provide summarized data in a format where data can be verified; 5) repeat statistical analysis for newly summarized data for 1982 alone, 1983 alone, and the combined 1982-83 data.

Hall - Study II: The data relating to this submission were reviewed by me 10/16/84. Additional statistical analysis has now been performed. The main problem remains - - the ribavirin group had higher illness scores at the beginning of study and there was no significant difference at end of study. Incremental improvement could be attributed to treatment or to differences in the natural history of more severe disease. Virologic efficacy was demonstrated if data can be provided that show stability of ribavirin at 65°C for 30 minutes. Additional data were analyzed, but no differences between groups were reported other than incremental differences. Clinical efficacy has not been demonstrated by further analysis of the Hall II data.

McIntosh - 1982-1984: The data relating to this submission were reviewed by me 10/16/84. Additional statistical analysis has now been performed. Other problems noted 10/16/84 remain. Additional data were analyzed, but no differences between the groups were reported other than incremental differences. Efficacy based on a meaningful clinical endpoint has not been shown.

Parrott: This is a copy of the summary previously reviewed by me 10/16/84.

Overall Summary: Data and statistical presentation differ for each study. Different measures were chosen for statistical presentation for each study even when data were uniformly available. What does NR mean? Table 6 - Values of 62.43 and 62.43 cannot differ with p = 0.47. Some data on this table is $P_aO_2$ amd some $S_aO_2$. The clinical relevance of incremental changes in parameters which themselves cannot be shown to differ between the groups is highly questionable. The large number of statistical analyses without a previously stated hypothesis is likely to lead to apparently significant differences on a random basis.

1985 SPR Abstract Submission:
Dr. Rodriguez, et al. The data from the same study were reviewed 10/16/84. No statistically and clinically significant differences were reported then. No antiviral effect was noted. Now statistically significant incremental changes are claimed. The data cannot be readily verified from the case report forms in their present format. The clinical significance of the incremental changes is dubious.

Dr. Taber 1981-82: Previously reviewed by Dr. Canchola, November 1983. Then, as now, no case reports are provided. Although "blinded" observations are reported, it is not stated that a placebo was used. The only significant difference claimed is for bronchiolitis severity, a subjective measure. For an efficacy claim to be based on a subjective measure, potential observer bias must be eliminated by the use of a placebo. No virologic efficacy demonstrated.

Edelson: The data for this submission were reviewed by me 10/16/84. A statistical analysis has now been performed. The following problems remain: 1) I cannot tell who received placebo from case reports or other investigator data; 2) No investigator data provided for RSV status of and 3) At least one RSV negative patient is included in analysis of efficacy of supplemental $O_2$; 4) Investigator's data for supplemental $O_2$ not shown or disagrees with summary (__ both admissions);5) admitted and enrolled twice in one month. First enrollment was unblinded. was switched to ribavirin open protocol after 7d, but recorded as having 15d $O_2$ as part of placebo group. was admitted twice and analyzed once. Data for 2nd admission do not explain why drug was discontinued and resumed and do not show duration of $O_2$ use. 6) RSV-IgE investigator data are not shown.

The sponsor will be asked to address these problems and present a corrected, verifiable summary.

Conclusion: Studies showing only incremental improvement in illness score, $S_aO_2$, or pulse do not provide clinically meaningful evidence of efficacy. Hall I and Edelson do not provide evidence of efficacy as submitted. If all problems in the latter studies are addressed by sponsor, efficacy may be demonstrated in fewer than 50 subjects. Because of ribavirin's activity in vitro and the opinion of many experts in pediatric infectious diseases, I believe this drug could be shown to be effective. However, data to support this belief have not been submitted to FDA.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/12/11/84
2536b

QT 12/18/84

Medical Officer's Review (#3) of NDA 18-859
Admendment (34)

Received by Reviewer: 12/20/84
Completed by Reviewer: 12/27/84

Applicant: Virtek
22. North Vincent Avenue
Covina, CA 97122

Name of Drug: Ribavirin

Clinical Studies:

Hall - Study I:

1) This submission established that the investigator states that all control patients did receive a placebo (water) aerosol.

2) This submission explains satisfactorily how the 4 point illness scale data were merged with 10 point scale data.

3) However, the submission does not explain satisfactorily the basis for including infants with cardiovascular and/or lung disease. Several patients should have been excluded; however, they are equally distributed between the two groups.

4) Striking errors have been reported. Several cases have been mistakenly assigned to placebo or ribavirin group. This is said to be corrected in the present submission.

5) It is still not possible to verify illness scores for the admission day from the case report forms. These admission data are required to see if the differences on days four and five of therapy can be attributed to drug or if they may have been present before drug was administered. Day one data cannot be used because on day one the groups were different. The sponsor will be so notified.

6) The $PaO_2$ and $SaO_2$ data in this submission often do not agree with that shown on the case reports forms.

Overall Summary: (Amend. 19) UR can be used when data were not reported. However, Table 2 and other tabulated data are shown without statistical analysis, and this is unacceptable.

Conclusion: Sufficient data to verify efficacy claims are still lacking.

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-345/VSchauf/1/14/85

3744A

Medical Officer's Review (#3) of NDA 18-859
Admendment (34)

Received by Reviewer: 12/20/84
Completed by Reviewer: 12/27/84

Applicant: Viratek
222 North Vincent Avenue
Covina, CA 97122

Name of Drug: Ribavirin

Clinical Studies:

Hall - Study I:

1) This submission established that the investigator states that all control patients did receive a placebo (water) aerosol.

2) This submission explains satisfactorily how the 4 point illness scale data were merged with 10 point scale data.

3) However, the submission does not explain satisfactorily the basis for including infants with cardiovascular and/or lung disease. Several patients should have been excluded; however, they are equally distributed between the two groups.

4) Striking errors have been reported. Several cases have been mistakenly assigned to placebo or ribavirin group. This is said to be corrected in the present submission.

5) It is still not possible to verify illness scores for the admission day from the case report forms. These admission data are required to see if the differences on days four and five of therapy can be attributed to drug or if they may have been present before drug was administered. Day one data cannot be used because on day one the groups were different. The sponsor will be so notified.

6) The $PaO_2$ and $SaO_2$ data in this submission often do not agree with that shown on the case reports forms.

Overall Summary: (Amend. 19) UR can be used when data were not reported. However, Table ? and other tabulated data are shown without statistical analysis, and this is unacceptable.

Conclusion: Sufficient data to verify efficacy claims are still lacking.

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:ls/1/14/85

Medical Officer's Review #4 of NDA 18-859
Amendment No. 30, 31, 33, 36

Applicant: Viratek
222 North Vincent Ave.
Covina, CA 97122

Name of Drug: Ribavirin

Clinical Study:

Dr. Taber 1981-82:

Previously reviewed by Dr. Canchola, November, 1983 and by me December, 1984. For the first time, case report forms have been provided. Many of the are poorly labeled as to who made the observations, whether or not the observations were blind, and which days and dates of illness the observations took place. The only significant difference claimed is in day 3 bronchiolitis severity, a subjective measure. The present submission documents the use of a placebo. However, many of the recorded bronchiolitis scores are by the "unblinded" observer. For example, "blind" bronchiolitis scores are available for days 0, 1, 2, and 3 for only 3 of 14 placebo recipients and for none of 12 treated subjects. This clinical data formed the basis for an article in Pediatrics 72: 613, 1983. There is some discrepancy between the article and my own review based on the blinded case report data as follows:

Blinded Day 3 Bronchiolitis Score

| | Taber et al., Pediatrics, 1983 and NDA Vol. 1.3 p A1004-6 | | FDA reviewer | |
|---|---|---|---|---|
| | No. patients | Mean Score | No. Case reports | Mean Score |
| Ribavirin | 7 | .6* | 8 | .8** |
| Control | 10 | 1.3* | 11 | 1.4** |

* - P = 0.044 Wilcoxon rank sum test, 2-tailed

** - P = 0.074 Wilcoxon rank sum test, 2-tailed

An antiviral effect was not detected during study days 0-4. Convalescent RSV neutralizing antibody titers were higher in controls than in ribavirin recipients. The basis for this difference is unknown. Possible explanations are: 1) more or longer viral replication in controls, or 2) suppression of B cells in ribavirin treated subjects. It is not known whether this antibody would be protective, would mediate immunopathologic lesions or would have no effect.

Conclusion: The evidence for ribavirin efficacy in the Taber study is marginal at best.

Dr. Edelson:

Previously reviewed by me 10/84 and 12/84. The efficacy claim was based on decreased requirement for supplemental $O_2$ in ribavirin (5) as compared to placebo (6) subjects in the high risk group. However, the ribavirin group does not contain 5 evaluable subjects, as noted below:

1) did not have RSV + culture or IFA.

2) was hospitalized only one day according to case report forms and p. 884, vol. 5.5 of NDA. Therefore, 4 days supplemental $O_2$ use cannot be verified and treatment can have taken place for no more than one day.

Additionally, (placebo) has no data shown to support RSV infection. There are too few evaluable patients in ribavirin group on whom to base an efficacy claim. The importance of the possible ribavirin effect on RSV-IgE is unknown since the role of RSV-IgE in the pathology of RSV disease is speculative at present.

Conclusion: The Edelson study does not support the sponsor's claim of efficacy.

Hall I:

Previously reviewed by Dr. Canchola 11/83 and by me 12/18/84 and 12/27/84. The present submission (Amendment (36)) summarizes baseline illness scores. Placebo and ribavirin subjects did not differ at baseline. Thus, it is very likely that the difference in illness scores during treatment is due to ribavirin. Data have also been submitted (Amendment (31)) from an experiment conducted at Baylor in December, 1984 which supports the claim that ribavirin is heat stable at 65°C for 30 min. These data support Dr. Hall's conclusion that an antiviral effect was shown and was not an artifact produced by carry over of ribavirin in nasal wash. Previous submissions did not satisfy this point.

Conclusion: Hall I constitutes a well-controlled demonstration of both clinical and virologic efficacy of ribavirin.

Summary of Clinical Studies:

(1) Hall I - Demonstrates ribavirin efficacy.

(2) Hall II - Groups differed at baseline in illness severity. Only incremental changes from baseline were shown.

(3) McIntosh - The claim for efficacy is based on a 1.7 point advantage on a 22 point artificial scale, is miniscule, and is not a meaningful clinical endpoint. This scale was partially subjective and no placebo was used. The claim for antiviral efficacy was based on viral antigen detection, not culture of infectious virus.

(4) Parrott - The statistically significant temperature differences are trivial and of no clinical importance.

(5) Taber 1981-1982 - Marginal evidence for efficacy in bronchiolitis score (0.8 vs 1.4, p = .074). Possible effect on RSV neutralizing antibody.

(6) Taber 1983-1984. Not evaluated for efficacy.

(7) Edelson - Only 3 ribavirin subjects are evaluable in group for which efficacy is claimed. Possible effect on RSV-IgE antibody.

(8) Sponsor summary of 11-20-84. Claims of efficacy based only on differences in improvement in parameters which themselves cannot be shown to differ between the groups is not clinically meaningful.

Although ribavirin may be effective for RSV infection, the sponsor has, with one exception, submitted studies almost guaranteed to fail to show efficacy because of their design, implementation, and/or reporting.

Some examples of the problem follow:

1) Very small numbers for study groups (e.g. Edelson).

2) Heterogeneous protocols and study populations preclude pooling data from small studies (e.g. McIntosh/Edelson).

3) Randomization hard to achieve with very small numbers (e.g. Hall II).

4) Pressure to put "sick" babies on compassionate use prototcols instead of randomizing, resulting in small, selected populations for controlled studies (e.g. Hall II).

5) Lack of clearly stated hypothesis to be tested. Use of subjective endpoints.

6) Failure to determine that drug concentration delivered to site of infection is virustatic.

7) Varied modes of drug delivery. Difficulties in administration per ventilator ("rain-out", pressure effects) (e.g. McIntosh).

8) Possible instability of drug during manufacture of final dosage form.

9) Study designs with unequal numbers in control and treatment group make it harder to achieve statistical significance (e.g. Parrott).

10) Incomplete and inaccurate recording of data on case report forms (all studies).

Even Hall I, which was acceptable for proof of efficacy, required multiple requests from FDA to sponsor to provide the necessary supporting data. Safety monitoring was very limited in all the clinical studies.

Recommendation:

(1) Disappproval unless Dr. Taber can satisfactorily explain discrepancies in data in Pediatrics versus case report form data.

(2) Any new studies should take into account the detailed critique listed above.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA GT 2/7/85
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/1/17/85
2843b

cRD 25Jan85

Medical Officer Review (#5) of NDA 18-859

March 13, 1985

Applicant: Viratek
22 North Vincent Avenue
Covina, CA 97122

Name of Drug: Ribavirin aerosol

Pharmacology Reviews by Norma Browder, Ph.D.

Dr. Browder has reviewed ribavirin aerosol as follows:

18-859 - 3/26/84
18-859 - 7/29/83

Additional pharmacology reviews of preclinical studies of ribavirin were prepared for NDA 18-266 and Developing lung study in ferrets is still incomplete and, thus, not reviewed.

Pharmacology

This agent is virustatic in vitro against a broad spectrum of viruses, including respiratory syncytial virus. The mode of action is unknown; however, intracellular nucleotide pools are perturbed, and viral RNA polymerase may be affected, as well as viral m-RNA. Pharmacokinetic data in humans are extremely limited partly because of difficulties in assaying for ribavirin in biological specimens. Using a RIA, Connor reported results in Lassa fever patients of McCormick receiving 1000 mg/d (15 mg/kg/d) PO in three divided doses. Mean concentration for four subjects 2.5 h post-dose was 31 uM. Lassa patients treated IV achieved mean plasma concentrations of 94 uM after 1000 mg doses and 68 uM after 500 mg doses. Long-term ribavirin aerosol therapy in pediatric patients led to plasma levels similar to those achieved with 1000 mg/d PO. Studies of ribavirin aerosol showed plasma half-lives of 6.5 - 11.0 hours. Longer half-lives have been reported with other regimens. It is suggested that the long half-life may be explained by a three compartment model with slow release into plasma and clearance by kidney; however, there are no data available to the reviewer to substantiate this possibility. Data to support use of the RIA for ribavirin quantitation are incomplete. (See pages 2-3).

The drug is metabolized and metabolites are excreted primarily in the urine of experimental animals. No data on metabolism/excretion in man are available to this reviewer. There is evidence for accumulation of ribavirin in RBCs in man and in experimental animals. This accumulation may be responsible for the hematologic toxicity of the drug.

No effect levels for parenteral, oral, or aerosol ribavirin have not been established in any species of animal. Thus, the pharmacology reviewer could not recommend an appropriate dose for human use. Even if a dose were established, without a well-established ribavirin assay, it would be a problem to determine the bioavailability of the aerosolized material.

Hematologic toxicity occurred at 30 mg/kg/d in monkeys receiving parenteral ribavirin and at 30 mg/kg/d in dogs receiving enteral ribavirin in subacute toxicity studies. In these dog studies, marrow effects were detected at the same dose. In subacute studies, low doses of ribavirin produced embryotoxicity, fetal deaths, and teratogenic effects in rodents. Effects on retina, myocardium, and epicardium were also noted.

In chronic studies, enteral doses of 30 mg/kg/d produced hematologic toxicity in rats and monkeys and 16 mg/kg/d produced gonadal toxicity and affected the thymus in rats.

Squirrel monkeys treated with 40 mg/kg/d ribavirin aerosol for 22 hr/d for 4 days showed increased respiratory rates, anemia, and histopathology noted in liver, kidney and pancreas. Chronic toxicity studies of the aerosol in the developing ferret lung have not been completely reported to FDA.

Carcinogenicity and mutagenicity studies are still in review; the drug is mutagenic and carcinogenicity has not been ruled out.

Ribavirin has both increased and decreased immune responses in experimental animals and in man.

Amendment 42

Sections 1-5 Ribavirin RIA and pharmacokinetic studies

Investigator pharmacokinetic data have been submitted and do confirm the published case reports. The reported ribavirin concentrations determined by RIA are limited to a few subjects. During a pharmacokinetic study, aerosol was discontinued in one subject due to cyanosis, respiratory distress and possible seizure. No form 1639 was submitted. Pre-dose specimens contained ribavirin in two subjects. Respiratory tract secretions contained extremely high concentrations during treatment (as high as 113,000 uM). One subject received "hand nebulized" ribavirin; the reasons for this and for discontinuing administration by respirator are not given. Death occurred during this treatment; however, no explanation or form 1639 were submitted.

The ribavirin RIA was not compared to another analytic technique to determine sensitivity and specificity. However, standard concentrations of 1-10 pmoles/100 ul were reproducibly detected. Some baseline (pre-drug) specimens have been reported to contain ribavirin, indicating either nonspecific reaction in RIA or mistiming of the specimen. The assay does detect at least one ribavirin metabolite.

Conclusion: Pharmacokinetic data are very scant and determined by an assay which has not been shown to be specific for the drug. Respiratory tract concentrations of ribavirin during aerosol treatment are astronomical. In experimental animals, ribavirin was toxic to embryos and fetuses and was teratogenic. The pre-clinical and clinical toxicities so far are consistent with the effects of the drug on nucleic acid metabolism. Until further animal data are obtained, ribavirin administration should be limited to patients at high risk, to those who do not have self limited disease, or to small numbers of well-informed volunteers for research. Monitoring should include CBC with red cell indices; bone marrow examination and haptoglobin determinations should be performed when anemia develops.

Amendment (41) SPAG-2 Manual

See reviews from HFZ-430. In addition, the final manual should include the final ribavirin package insert. The manual should specify how often the equipment should be cleaned and sterilized and how it should be monitored for contamination by potentially pathogenic nosocomial organisms (e.g. Pseudomonas aeruginosa). It should be specified how the non-autoclavable connections should be sterilized. A warning should be inserted to indicate the necessity for air to be supplied when the aerosol is in use. "Breathing air" should be defined. It should be specified how often the one-way valve in the inspiratory line should be changed. The effect of turning off the drying chamber (as recommended for use with ventilators) on aerosol size, drug delivery, and bioavailability need to be assessed. In the manual, there should be discussion of how to deal with the problems of rainout and of using equipment in patients with extreme tachypnea.

Conclusion: The November, 1984 SPAG2 Manual requires revision as noted above.

Clinical Background: Ribavirin has been studied in aerosol forms for a wide variety of human infections, including herpes simplex, hepatitis, respiratory syncytial and parainfluenza virus infection, and Lassa fever. The drug is licensed in many countries. To date, there has been little toxicity reported with ribavirin use. An just received by this reviewer says that subjects receiving high IV doses for Lassa fever experienced a 20% reduction in hematocrit; data were not submitted. Anemia has been reported to occur both as a result of hemolysis and of marrow depression.

Experience with ribavirin has recently been summarized and/or referenced in CLINICAL APPLICATIONS OF RIBAVIRIN, a book based on a symposium sponsored by Viratek and edited by some of the developers of the drug, Robert Smith and Vernon Knight (Academic Press, 1984). (Dr. Knight is also reported to have a financial interest in the aerosol drug, because of his role in developing the delivery system).

Related INDs and NDAs

Clinical Studies, Efficacy - See MORs (#1-4) and Dr. Canchola's NDA review of 11-14-84 for additional reviews of clinical studies.

Dr. Taber study 1981-82:

Met with Drs. Taber, Knight, Gilbert, and Fernandez regarding discrepancies between FDA review of their data (See MOR #4) and Pediatrics' article and summary submitted to FDA. The investigators provided an acceptable explanation for their data summary, and I now accept their data, as follows:

Blinded Day 3 Bronchiolitis Score

| | No. Patients | Mean Score |
|---|---|---|
| Ribavirin | 7 | .6 |
| Control | 10 | 1.3 |

The previous discrepancies occurred because a clear definition of day 0, day 1, etc., had not been provided to FDA or to the blinded observer. Using this definition and dates on the case report forms, the data could be verified.

These data provide evidence for the efficacy of ribavirin aerosol for bronchiolitis due to RSV infection.

Conclusion: Hall I (See MOR 3 and 4) and Taber 1981-2 show that ribavirin aerosol is effective for infants with lower respiratory tract infections due to RSV infection. Although the statistical reviewer has some valid statistical criticisms of these studies, the overall clinical conclusion is that they are acceptable for demonstrating efficacy.

Clinical Studies, Safety

Experimental Respiratory Syncytial Virus Infections in Young Adults. Hall, et al 1981.

Placebo and ribavirin aerosol groups were similar before and after 3 days treatment as judged by safety parameters, including CBC and SMA-12.

FVC was reported to decrease after ribavirin; however this result and other pulmonary functions were claimed not to differ significantly between placebo and ribavirin recipients. First and last RSV isolates from the subjects had similar sensitivity to ribavirin. Case report forms had no place to record virology data, pulmonary function results, or adverse reactions.

Conclusion: The drug did not affect CBC or SMA-12 and there was no adverse effect on lung function in normal adults. Resistance to ribavirin did not occur.

RSV Infections in Children
Hall, et al. 1982 (First year of Hall I).

No safety data or adverse reactions recorded on case report forms or in summary. These have been requested from Viratek without response.

Hall, et al. 1983 (Second year of Hall I)

Case report forms have no place to record adverse reactions. Few subjects had blood work after admission.

Hall I Conclusion: Submission does not provide adequate data to support claim of safety.

McIntosh, 1982-1983.

When ribavirin was delivered via a Health-Tyne time-cycle pressure limited ventilator, an enormous amount of fluid "rained out" in the tubing before reaching the patient. The pressure wave was significantly altered by the nebulizing apparatus. Gas exchange improved while off the nebulizing equipment. The effect of humidification on the aerosolyzed particles may be to preclude its delivery to the lung. Limited data on CBC and blood chemistry were unremarkable.

Conclusion: Significant difficulty was encountered using ribavirin aerosol for ventilated subjects.

Taber 1981-82

CBC and chemistry were studied at admission, discharge, and follow-up in ribavirin and placebo recipients. There were no important differences between the groups at any time for any parameter. The data from the case report forms agreed with the summarized data.

Conclusion: No toxic effects were noted as judged from CBCs and chemistries.

Hall II, 1983-4:

No safety data are summarized. This has been requested of the sponsor repeatedly. Almost no repeat blood work was done. In one case a repeat hematocrit showed a 10 point (25%) drop, and no explanation or discussion is given.

Conclusion: This submission does not support the sponsor's claim of ribavirin's safety.

Taber III, 1983-4:

No case report forms have been provided. However, the summarized results of CBCs and chemistries for 20 subjects did not show any important abnormalities.

Amendment 42 - Section 6

Summary of safety data from several clinical trials showed the following new information:

1. Parrott and Edelson trials - no significant difference before and after ribavirin for mean hemoglobin, hematocrit, SGOT, SGPT, bilirubin or BUN.

2. Marked reticulocytosis after ribavirin in 2 subjects (8.3, 6.3) from Knight and Edelson trial. Reticulocytes not summarized for Parrott study.

Compassionate Use

Summary of data from 86 compassionate use cases states there is "no evidence of side effects or adverse reactions attributable to ribavirin therapy". However, case reports note the following events which are associated with ribavirin use and cannot be attributed to other causes with certainty. Therefore, these are possibly related to ribavirin. These events include: pneumothorax (3), hypotension (2), death (2), cardiac arrest (1), increased $O_2$ requirement or other worsening in blood gases or respirator settings (6), apnea (1), clinical and/or radiologic deterioration (1), relapse (1), or development of respirator dependency (1). In addition, three physicians reported lack of efficacy and two* reported technical problems with delivery of the drug.

Conclusion: The sponsor is not entitled to claim no side effects or adverse reactions. Further data are required to determine the frequency and significance of these problems. The drug clearly lacks efficacy in some patients.

*One of these physicians was this reviewer. The experience occurred prior to joining FDA. The report was made after joining the FDA.

Amendment 42 - Section 5

At my request, Viratek surveyed some of its physician investigators and provided responses from Drs. McIntosh, Edelson, Hall, Rodriequez and Knight as follows:

1. Ribavirin resistance has not been observed in any of 4 serial RSV isolates from an immunodeficient child over two months during which three courses of aerosol treatment were administered (McIntosh, data not submitted); in any of 70 RSV isolates before, during, or after ribavirin treatment (Hall, data not submitted); or for (Knight, number specimens and data not submitted). For the $TCID_{50}$ in posttreatment specimens was twofold higher than pretreatment (Knight, number specimens and data not submitted).

   Conclusion: Resistance of RSV to ribavirin has not yet been observed. Further observation, post-marketing, would be important.

2. Ribavirin (or placebo) was discontinued during trials (but not specifically reported to FDA until now) because of rash (one child, not necessarily ribavirin related as other drugs were also given), clogging of respirator tubing (one child), lack of clinical improvement and transfer to open drug (one placebo, one ribavirin recipient), cardiac arrest due to apnea (one child, first in control group, then open drug), extreme tachypnea making interfacing with ventilator difficult (one child, who died a "few days" later). Not reported here in response to my query is a child who had ribavirin discontinued because of cyanosis.

   Conclusion: Although the sponsor claims no adverse reactions or problems have ever occurred with ribavirin, ribavirin therapy has been discontinued for the following reasons: rash, cyanosis, lack of clinical improvement, cardiac arrest due to apnea, clogging of respirator tubing, extreme tachypnea causing difficulty interfacing with ventilator. Although none of these events are definitely attributable to ribavirin, only one (lack of clinical improvement) was reported in a control patient. Further observation will be mandatory.

3. Two patients experienced pneumothorax while receiving ribavirin, during trials, although pneumothorax was not attributed to ribavirin in either case. None was reported in controls. Other cases of pneumothorax occurred in compassionate use cases.

Conclusion: Further observation for pneumothorax is mandatory.

4. There are no data concerning interaction of ribavirin with frequently used concomitant medications such as antibiotics or bronchodilators. Case report forms did not have a place for concomitant medications.

   Conclusion: Studies should be undertaken to assess possible drug interactions.

5. No data showing effect or lack of effect of ribavirin on respirator settings has been submitted.

   Conclusion: Data are required regarding effect of ribavirin on respirator settings. This could be obtained from compassionate use cases before, during, and between ribavirin administiations.

6. No data have been submitted concerning long term safety as judged by pulmonary function tests. Drs. McIntosh and Hall have pointed out the necessity of such studies.

   Conclusion: Infants in ribavirin protocols should be recalled for pulmonary function tests as soon as they are old enough to cooperate. Infants studied in 1982 may be old enough to participate even now.

7. Dr. McIntosh raises the issue of occupational exposure to ribavirin. This is of particular concern for pregnant women because of the teratogenicity of the drug.

   Conclusion: Blood of personnel caring for recipients of ribavirin aerosol should be measured for ribavirin. This should be done now in centers with multiple compassionate use cases.

   Form 1639: The sponsor claims "no adverse reactions noted in any treated patients".

   Conclusion: This is incorrect as noted above.

Pulmonary Function Studies: No investigator data have been provided, in spite of several requests to the sponsor. The sponsor's summary, taken directly from Hall et al. JAMA 249:2668, 1983, indicated minimal or no changes due to ribavirin in pulmonary function values before and after carbachol challenge of adults with experimental RSV infection. The sponsor claims that no adverse effect on pulmonary function occurs in infants treated with ribavirin, since they do no worse than other infants as judged by $S_aO_2$ and duration of illness. However, no functional meansurements have been made, and the clinical deteriorations noted in previous sections have not been acknowledged or explained by the sponsor. No measurements of pulmonary function were submitted in subjects with underlying lung disease. However, published reports (in CLINICAL APPLICATIONS OF RIBAVIRIN) do indicate a worsening of lung function with ribavirin. These data should be submitted.

Conclusion: Ribavirin has not been evaluated in a fashion which would detect adverse effects on pulmonary function if they did occur. Children from the treatment and control groups of the early ribavirin trials should be recalled for pulmonary function testing. Pulmonary functions should be measured before, during, and after treatment in future study and compassionate cases who are old enough to cooperate. Case report forms should be designed prospectively and allow for description of patient clinically and by blood gas determination and ventilator settings before, during and after ribavirin. Data on hand from asthma and COPD should be submitted.

Amendment (#42 - Section 15)

The sponsor claims that condensation in the inspiratory line of respirators resulting from use of highly humidified gases plus cooler air from SPAG-2 is unavoidable and of "little or no clinical significance." This claim is unsubstantiated.

Conclusion: The effect of rainout on ventilator and pulmonary performance should be measured in subjects by recording ventilator settings, blood gases, and pulmonary physical findings in the presence and absence of rainout due to ribavirin use. Additionally, the effect of rainout on drug delivery and bioavailability needs to be measured.

Overall Evaluation and Conclusions: Ribavarin aerosol efficacy and safety have been demonstrated in the following adequate and well-controlled studies:

1) Hall I - Infants with lower respiratory tract infection due to RSV had significantly lower illness scores and viral titers in ribavirin group as compared to placebo group.

2) Taber/Knight - 1981-2 - Infants with bronchiolitis due to RSV had significantly lower bronchiolitis scores on day 3 in ribavirin group as compared to placebo group. There was no hematologic, hepatic, or renal toxicity associated with ribavirin use.

3) Hall - Adults with experimental RSV infection treated with ribavirin had a decreased proportion with viral shedding days on 6-9 as compared to those treated with placebo. No changes in pulmonary function (data not submitted) or toxicity (CBC, SMA-12) were noted. Systemic symptoms and fever were less in ribavirin than in placebo recipients.

Supportative efficacy data come from Hall II and McIntosh which showed decreased viral titers and viral antigen respectively in the ribavirin group as compared to the control group. Supportive safety data came from the Parrott and Edelson trials (hematology and liver function).

Recommendations This NDA is approvable if the following deficiencies are satisfactorily addressed:

1. Provide satisfactory data so that the carcinogenicity of ribavirin in suitable experimental animals can be judged. This can be addressed post-marketing.

2. Provide complete data so that ferret study of developing lung can be reviewed. This can be addressed post-marketing.

3. Satisfy deficiencies noted by pharmacology (post-marketing) and chemistry pre-marketing) reviewers.

4. Revise SPAG-2 manual as indicated on p. 3, prior to an approvable letter being sent.

5. Assess effect on drug delivery of turning off drying chamber (as recommended for use with ventilators). This needs to be addressed immediately.

6. Prior to an approvable letter, submit data prospectively collected from study and compassionate use subjects before, during, and after ribavirin or placebo as follows: time treatment begun, time ended, timing of interruptions of treatment, pulse, respiratory rate, temperature, respiratory effort, presence or absence of cyanosis, retractions, grunting, apnea, pneumothorax, hypotension, cardiac arrest, death; blood gases; development of respirator dependence; respirator settings, PEEP, occurrence of rainout, collection of crystals in respiratory equipment, use of SPAG-2 drying chamber; any adverse effect not definitely explained by something other than ribavirin or SPAG-2 in the investigator's opinion.

7. Report all patients for whom ribavirin aerosol protocols or compassionate use had to be discontinued before the course was completed and give reason why. This must be addressed immediately.

8. Prior to issuance of an approvable letter, submit a Safety Update including all adverse effects to date not definitely explained by something other than ribavirin or SPAG-2 in the physician's opinion. Commit that they will submit in their annual reports all adverse effects to date not definitely explained by something other than ribavirin or SPAG-2 in the physician's opinion.

9. Some subjects from the earliest trials are now old enough to cooperate for pulmonary function testing. They should be evaluated to assess long term safety in developing human lung. $S_aO_2$ alone is not sufficient.

10. Submit investigator data on lung function with ribavirin in asthma and COPD, prior to receiving an approvable letter.

11. Because ribavirin is teratogenic and is administered by aerosol, personnel caring for recipients (and/or those exposed in its manufacture) should have blood assayed for ribavirin during and after exposure. Between 20 and 40 people should be studied, pre- or post marketing. If no drug is absorbed, no further studies would be needed.

12. Justify the claim that rainout with ventilator and SPAG-2 is "unavoidable" and of "little or no clinical significance," prior to receiving an approvable letter.

13. Prior to receiving an approvable letter, summarize in verifiable format and provide investigator data to show whether or not dilutional hyponatremia or weight gain occurs with use of SPAG-2 with or without ventilator. Alternatively, collect this data prospectively.

14. Because of its mutagenicity, teratogenicity, and potential carcinogenicity, ribavirin aerosol use should be limited to patients with underlying diseases known to put them at high risk and to those who do not have self-limited disease. In research protocols, use should be limited to small numbers of well-informed volunteers.

15. Submit a protocol for compassionate use of ribavirin for subjects who do not have an indication for ribavirin.

Items 3-8, 10, 12, and 13 above explained to Dr. Staffa during telephone conversations on 3/12/85.

In addition, it would be important for this and future ribavirin INDs and NDAs to have the following satisfactorily addressed:

1. Improve specificity of RIA for ribavirin or develop more satisfactory assay.

2. Assess potential gonadal toxicity in human.

3. Determine if any physical, chemical, pharmacologic, toxicologic, or virologic interactions occur between ribavirin and other drugs which are frequently used in the settings proposed for ribavirin.

4. Assess anemia if it occurs with ribavirin use with haptoglobin determinations and bone marrow examination.

5. Prospectively develop case report forms for all studies. Provide space to record all adverse reactions during treatment and space to indicate the investigator's opinion of the role of ribavirin in the adverse reaction (definite, probable, possible, definitely no role).

6. Increase surveillance for ribavirin resistant viruses.

7. If it is intended to extend indications to include patients with self-limited RSV lower respiratory tract disease, provide an explanation and data as to how ribavirin could be used without greatly increasing costs, by extending the hospital stay, virology laboratory costs, or the rate of hospital admission for children with mild-to-moderate disease. Alternatively, justify such increases. Indicate how this would affect labeling.

8. Provide bioavailability data for aerosol delivered by mask, hood, and endotracheal tube in neonates, infants, children, and adults.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/3/8/85
3352b

DHO 22Mar85

3/28/85

Division Director's Comment

Labelling meeting scheduled for next week should be postponed until the company submits the safety data requested several weeks ago. There is no possible way that labelling can be developed without this information.

Dr. Schauf states that she believes additional safety data from the two Hall studies does not exist. S. Read, M.D.

NDA 18-859 ✓

Addendum to MOR (#5)

March 28, 1985

Sponsor: Viratek
222 North Vincent Avenue
Covina, CA 91722

Name of Drug: Ribavirin (Virazole) Aerosol

1. Taber 1981-2.

I held a meeting with the investigators and sponsor to examine the apparent discrepancies between their report of their data and my review of it. They explained that the blind observer and I had used a different way of determining the study day than had been used in the data analysis. In the former case, day one was the first 24 h on drug. In the latter case, day 0 was the calendar day treatment was begun (ending at midnight) and day one was the calendar day after day 0. Using the latter definition, my review of the cases agrees with the data summary submitted to FDA.

2. As noted in MOR (#5,) the McIntosh study indicates a decrease in RSV antigen in ribavirin as compared to placebo recipients and supports the claim of efficacy. However, on further review, much of the RSV antigen data is missing from the case report forms. To verify this claim, I have requested the data from the sponsor.

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/3/28/85
3534b

Medical Officer's Review (# 6) of NDA 18-859

AMENDMENT (48)

Name of Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, California

Name of Drug: Ribavirin (Virazole) Aerosol

This submission is a revision of the SPAG-2 manual (Amendment 41). This reviewer has still not been able to see the review from HFZ-430. Dr. Taylor is also reviewing Amendments (41 and 48). (Most of the deficiencies noted in MOR #5 (3-13-85) and conveyed to Dr. Staffa by me on 3-12-85 by telephone remain. Further deficiencies have become evident in the present review.)

Recommendation:

Before an approvable letter is sent, satisfy the following:

1. Add a warning to indicate the necessity for air to be supplied when aerosol is in use in section G as well as section H. Label both so that they stand out and will not be missed.

2. Althought it is stated that "the wetted parts are sterilized after each use", it is not clear what is meant by "use". Daily sterilization would be a minimum requirement.

3. Specify what kinds and concentrations of disinfectants are suitable for cleaning after patient use.

4. Add to the SPAG-2 manual the response that hospital personnel should follow standard or established procedures for monitoring bacterial contamination of nebulizers and that "no special or additional monitoring" is required for the SPAG-2.

5. Put a section in the SPAG-2 manual for the Virazole package insert.

6. Specify procedures for sterilizing the connector that cannot be autoclaved. Provide data that this procedure is effective and does not damage the connector.

7. The revised manual has no figure or diagrams. Indicate if these are to be the same as in Amendment 41.

8. Indicate how often the one-way valve needs to be monitored for precipitation.

9. Provide data concerning the aerosol produced with the drying chamber off, including: ug drug/liter aerosol and particle size. Explain what MMAD number means and provide data to show this number with and without drying. Explain the statement and provide data to support the statement that "the absence of drying air flow should not unduly hamper the efficiency of the SPAG-2 finished device." If this is so, explain why the drying chamber is incorporated in the SPAG-2. Respond, as previously requested, to the question "How does use of the drying chamber affect bioavailability?"

10. Respond, as previously requested, by providing in the manual a discussion of how to use SPAG-2 in patients with extreme tachypnea. Alternatively, state that such use is contraindicated and label the statement accordingly.

11. Justify the absence of a water trap in the SPAG-2 outflow lines.

12. Identify and explain the revisions in Amendment(48) which were not in response to my review.

13. It will be necessary to remove from the manual all the parts referring to the ventilator and to add a warning "Not to be used with ventilator" unless safety concerns and data previously requested and not yet received support this use.

14. Explain how SPAG-2 is to be connected to and used with a hood, tent, and face mask. Provide suggested air flows for each mode of delivery.

15. Indicate that compressed gas means air mixed with varying amounts of $O_2$, if this is the case.

16. Do you mean apparent flow rate rather than "relative" when discussing nebulizer air flow? If so, say so. If not, explain.

17. Indicate need for tubing not provided with machine. Indicate how often does the tubing needs to be changed.

18. Indicate how often Virazole needs to be reconstituted and how often remaining solution should be discarded. Indicate expected ribavirin concentration at end of use interval.

19. Explain why SPAG-2 cannot be built so that external knob for nebulizer flow meter valve does not "disconnect."

20. Provide data to show how varying flow between 12 and 15 LPM influences particle size, drug delivery, and bioavailability.

21. Explain why drying air should be off with ventilator (if this is to be included). Explain why in some instances a minimal flow is desired. Provide same data requested in 9 for this minimal flow (1-2 LMP).

22. Provide data to show effect of "one tidal volume" on particle size, drug delivery, and bioavailability, if ventilator use is to be included. Similarly, provide data to show effect of condensation on particle size, drug delivery, and bioavailability.

23. Give an example of the kind of one-way valve that is to be used. Indicate that this is to be provided by the hospital. Indicate if it should be sterile.

24. If ventilators are to be included, provide data to show how much PEEP increase is expected from drug precipitation. Indicate this in manual and specify possible consequences of increased PEEP (pneumothorax, decreased pulmonary function). Add a noticable warning that PEEP should be carefully monitored and recorded every 15 minutes.

25. Give an example of the kind of bacterial filter recommended and indicate that this is to be provided by the hospital. Provide data to show whether or not filter affects ventilator function.

26. Put back in the next draft the section on use of $O_2$ blender.

27. Specify which components are to be washed.

28. Explain why cleaning procedure for nebulizer has been changed.

29. Indicate if the ICN telephones are answered on a 24-hour basis.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ST 4/5/85
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/4/85
3602b

Medical Officer's Review (# 6) of NDA 18-859

AMENDMENT (48)

Name of Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, California

Name of Drug: Ribavirin (Virazole) Aerosol

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Recommendation:

Before an approvable letter is sent, satisfy the following:

1. Add a warning to indicate the necessity for air to be supplied when aerosol is in use in section G as well as section H. Label both so that they stand out and will not be missed.

2. Althought it is stated that "the wetted parts are sterilized after each use", it is not clear what is meant by "use". Daily sterilization would be a minimum requirement.

3. Specify what kinds and concentrations of disinfectants are suitable for cleaning after patient use.

4. Add to the SPAG-2 manual the response that hospital personnel should follow standard or established procedures for monitoring bacterial contamination of nebulizers and that "no special or additional monitoring" is required for the SPAG-2.

5. Put a section in the SPAG-2 manual for the Virazole package insert.

6. Specify procedures for sterilizing the connector that cannot be autoclaved. Provide data that this procedure is effective and does not damage the connector.

7. The revised manual has no figure or diagrams. Indicate if these are to be the same as in Amendment 41.

8. Indicate how often the one-way valve needs to be monitored for precipitation.

9. Provide data concerning the aerosol produced with the drying chamber off, including: ug drug/liter aerosol and particle size. Explain what MMAD number means and provide data to show this number with and without drying. Explain the statement and provide data to support the statement that "the absence of drying air flow should not unduly hamper the efficiency of the SPAG-2 finished device." If this is so, explain why the drying chamber is incorporated in the SPAG-2. Respond, as previously requested, to the question "How does use of the drying chamber affect bioavailability?"

10. Respond, as previously requested, by providing in the manual a discussion of how to use SPAG-2 in patients with extreme tachypnea. Alternatively, state that such use is contraindicated and label the statement accordingly.

11. Justify the absence of a water trap in the SPAG-2 outflow lines.

12. Identify and explain the revisions in Amendment (48) which were not in response to my review.

13. It will be necessary to remove from the manual all the parts referring to the ventilator and to add a warning "Not to be used with ventilator" unless safety concerns and data previously requested and not yet received support this use.

14. Explain how SPAG-2 is to be connected to and used with oxyhood, tent, and face mask. Provide suggested air flows for each mode of delivery.

15. Indicate that compressed gas means air mixed with varying amounts of $O_2$, if this is the case.

16. Do you mean apparent flow rate rather than "relative" when discussing nebulizer air flow? If so, say so. If not, explain.

17. Indicate need for tubing not provided with machine. Indicate how often does the tubing needs to be changed.

18. Indicate how often Virazole needs to be reconstituted and how often remaining solution should be discarded. Indicate expected ribavirin concentration at end of use interval.

19. Explain why SPAG-2 cannot be built so that external knob for nebulizer flow meter valve does not "disconnect."

20. Provide data to show how varying flow between 12 and 15 LPM influences particle size, drug delivery, and bioavailability.

21. Explain why drying air should be off with ventilator (if this is to be included). Explain why in some instances a minimal flow is desired. Provide same data requested in 9 for this minimal flow (1-2 LMP).

22. Provide data to show effect of "one tidal volume" on particle size, drug delivery, and bioavailability, if ventilator use is to be included. Similarly, provide data to show effect of condensation on particle size, drug delivery, and bioavailability.

23. Give an example of the kind of one-way valve that is to be used. Indicate that this is to be provided by the hospital. Indicate if it should be sterile.

24. If ventilators are to be included, provide data to show how much PEEP increase is expected from drug precipitation. Indicate this in manual and specify possible consequences of increased PEEP (pneumothorax, decreased pulmonary function). Add a noticable warning that PEEP should be carefully monitored and recorded every 15 minutes.

25. Give an example of the kind of bacteri. filter recommended and indicate that this is to be provided by the hospital. Provide data to show whether or not filter affects ventilator function.

26. Put back in the next draft the section on use of $O_2$ blender.

27. Specify which components are to be washed.

28. Explain why cleaning procedure for nebulizer has been changed.

29. Indicate if the ICN telephones are answered on a 24-hour basis.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ST 4/5/85
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/4/85
3602b

Medical Officer's Review #7 of NDA 18-8[illegible]

April 4, 1985

Amendment 49

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug: Ribaririn (Virazole) Aerosol

This submission is intended to respond to some of the safety issues raised in MOR (#5) and conveyed by me to Dr. Staffa by telephone on 3-12-85. (The submission is entirely nonresponsive to any of the issues raised. The submission largely repeats previous unsatisfactory submissions.)

A safety update was requested. Instead of this being provided, it is stated that "no evidence of side effects or adverse reactions have been reported in any patient receiving ribavirin aerosol." This restates the problem. The adverse reactions noted in MOR (#5) still have not been reported. No overseas data have been submitted. Several adverse experiences are described in the submission, but still are being discounted as noted above.

To determine if water overload is occurring with prolonged aerosol use in infants with immature renal function (as has previously been reported for mist tents alone), weights or sodium values were requested. Instead, plasma sodium before and after treatment were provided. Data are needed during treatment to assess this risk.

Conclusion: (This amendment is entirely nonresponsive to the safety issues which need to be addressed prior to an approvable letter.)

Recommendation: (Unchanged from MOR #5.)

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CCO
HFN-340
HFN-815/VSchauf:js/4/10/85
3666b

Medical Officer's Review #7 of NDA 18-859

April 4, 1985

Amendment 49

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug: Ribaririn (Virazole) Aerosol

This submission is intended to respond to some of the safety issues raised in MOR (#5) and conveyed by me to Dr. Staffa by telephone on 3-12-85. (The submission is entirely nonresponsive to any of the issues raised. The submission largely repeats previous unsatisfactory submissions.)

A safety update was requested. Instead of this being provided, it is stated that "no evidence of side effects or adverse reactions have been reported in any patient receiving ribavirin aerosol." This restates the problem. The adverse reactions noted in MOR (#5) still have not been reported. No overseas data have been submitted. Several adverse experiences are described in the submission, but still are being discounted as noted above.

To determine if water overload is occurring with prolonged aerosol use in infants with immature renal function (as has previously been reported for mist tents alone), weights or sodium values were requested. Instead, plasma sodium before and after treatment were provided. Data are needed during treatment to assess this risk.

Conclusion: (This amendment is entirely nonresponsive to the safety issues which need to be addressed prior to an approvable letter.)

Recommendation: (Unchanged from MOR #5.)

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/10/85
3666b

ET 4/19/85

NDA 18-859

Jackie Knight

Medical Officer's Review (#8) of NDA 18-859

April 4, 1985

Amendment 50

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug: Ribaririn (Virazole) Aerosol

This submission consists of an abbreviated protocol entitled, "Protocol for Obtaining Ribavirin Blood Levels from Environmentally Exposed Primary Care Nurses." This should have been submitted (to

As in other submissions, the misstatement that "patients treated with ribavirin by the aerosol route showed no adverse reactions" is prominent.

The pharmacology review is not available at the time of this writing.

No investigator has been identified.

No consent form has been submitted.

No case report form has been submitted.

The objective is to determine if nurses caring for patients receiving ribavirin aerosol absorb the drug. The rationale for this is that the aerosol for the patient is not contained and will escape into the environment. The significance is that the drug is teratogenic.

The experimental design is not adequately described. Is the "blood" sample serum, plasma, or RBC's? What is the timing of the specimen (beginning or end of shift)?

Conclusion: This hastily contrived protocol is likely to lead to negative results even if ribavirin is being absorbed.

Recommendations: Require a complete and satisfactory protocol be submitted (to including case report form, informed consent, description of samples to be assayed and their timing as a condition for an approvable letter for the NDA.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA, HFN-815 ET 4/19/85
HFN-815/CSO, HFN-340
HFN-815/VSchauf:js/4/10/85
3666b

YRO 11 Apr 85

Jackie Knight

Medical Officer's Review #9 of NDA 18-859

April 4, 1985

Amendment 61

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug: Ribavirin (Virazole) Aerosol

This submission consists of a protocol to collect data on the respiratory status of patients receiving ribavirin aerosol while on a ventilator. The patients will be those receiving ribavirin on a compassionate basis. Data will be collected every 2-4 h during treatment.

Data to be recorded include timing of ribavirin adminstration, ventilator settings, SPAG-2 drying chamber use status, vital signs, blood gases, timing of patient withdrawal from treatment, adverse reactions, problems wih SPAG unit.

Recommendations: Prior to receiving an approvable letter:

1. Submit the revised protocol.

2. Clarify on the data sheet that for each set of observations it is necessary to know how long the patient has been on or off the aerosol. When the patient is off aerosol, it is necessary to know whether or not this is a scheduled interruption. If not, the reason for the interruption needs to be given.

3. Include all observations except ventilator settings for compassionate cases which do not require ventilation.

4. All adverse reactions need to be reported on Form 1639 and in the NDA. The investigator must indicate whether or not the reaction is possibly, probably, or definitely related to ribavirin administration. Nofify the investigator that it is particularly important to look for the following: increased or decreased respiratory effort, retractions, grunting, apnea, pneumothorax, hypotension, cardiac arrest, death, development of respirator dependence, edema, weight gain, dilutional hyponatremia. Indicate if adverse reactions or problems with SPAG-2 unit resulted in stopping drug ahead of schedule.

5. For all patients indicate reason for stopping drug course (e.g. course completed, recovered, adverse reaction).

6. Indicate timing of ventilator use, including use before and after ribavirin course.

7. Add a space on the case report form to record weight and serum sodium.

8. Add this entire protocol to the compassionate use protocol (revision of Supp. 40,

9. Submit complete case report forms from at least 30 patients treated with ribavrin. It would be acceptable to attempt to collect some of this data retrospectively from ICU records for placebo and ribavirin patients already studied.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ST 4/19/85
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/10/85
3666b

Div 4/19/85

Division Director's Note

Some of this data [illegible] is available at Bayler, from the study and from hundreds of compassionate use cases, [illegible] to Dr. Ralph Feigin, Chairman of the Dept. of Pediatrics.

[illegible], M.D.

C-50

Medical Officer Review (#10) of NDA 18-859

April 22, 1985

Amendment 55

Sponsor: Viratek

Name of Drug: Ribavirin (virazole) Aerosol

McIntosh Study:

This submission is intended to respond to my request for original investigator data to support the statement in Dr. McIntosh's study, that ribavirin decreased RSV antigen in nasal secretions. If confirmed, this data would support the efficacy demonstrated in two small clinical trials by showing virologic efficacy.

The data in this submission disagree with that in the case report forms included in Amendment [illegible]. For example, results on the case report form for [illegible] (Patient [illegible]) are shown in this submission for Patient [illegible] and vice versa. Similarly, results on the case report form for [illegible] (Patient [illegible]) are shown in this submission for Patient [illegible].

The basis for correcting the O.D. measurement for protein content of the nasal secretion is not explained and differs from that in Dr. McIntosh's published method (J Clin Microb 16:324-333, 1982). It is stated that the corrections are based on the lowest protein reading from a "positive" specimen. However, the correction is needed before a specimen is "positive". "Positive" is not defined. The lowest reading was not always used. The range of protein content is enormous and there is no validation or data to support use of this correction over this range.

Conclusion: Because of the small size of the clinical trials showing efficacy, virologic confirmation from another study is very important. So far the data submitted do not provide this confirmation.

In addition, validation is required for the method for correcting OD over the range of protein concentrations used. Explain what a "positive" specimen is and why the lowest protein reading was not used in each case where it was not used (e.g. 83-4).

Light, Aoki Study:*

This submission includes material relating to the study subjects reported in Light, et al. "Tolerance of Ribavirin Aerosol Inhaled by Normal Volunteers and Patients with Asthma or Chronic Obstructive Airways Disease" published in CLINICAL APPLICATIONS OF RIBAVIRIN, Academic Press, 1984. Included are computer print-outs showing age, sex, height, baseline spirometry results and lung volumes and serial spirometry shown as % baseline. No case report forms were submitted, as had been requested. No data on normal subjects was included. Lung volume measurements during treatment were not included. Respirograph tracings were submitted. Presumably, these were used to calculate the results of spirometry. However, the calculations are not provided and the tracings are not standard ones.

By the investigators' published criteria, significant abnormalities are reduction of FVC or peak flow by 20% or more and reduction of FEV, or MMEF by 10% or more. By these criteria, ribavirin had an adverse effect on one or more of these parameters of pulmonary function for every COPD subject and for four of six asthmatic subjects. Even the placebo aerosol had an adverse effect in three COPD and two asthmatic subjects. The sample size is too small to conclude whether or not adverse reactions were significantly more frequent with ribavirin than with placebo aerosol. In any event, if the aerosol treatment without drug has an adverse effect on pulmonary function in already compromised patients, this must be taken into account in the risk/benefit consideration for such patients.

The computer print-outs disagree importantly from the published report. For example, two asthmatic subjects were reported to experience dyspnea with ribavirin and 46% and 25% reduction in $FEV_{1.0}$ and 39% and 32% reduction in MMEF. Only one of these four values appeared in the computer print-out. Most subjects have no investigator data as a basis for lung volumes shown in computer print-out. Potential adverse reactions noted on respirograph data have not been included in report. For example, "chest sore" is noted for one subject.

The dyspnea noted in subjects in the published report has not been reported to FDA; nor has it been noted in the sponsor's submission, which still proclaims "no adverse reactions."

Conclusion: The investigators have collected important data pertaining to the safety of ribavirin aerosol. The sponsor has been negligent in reporting the data to FDA.

* $FEV_{1.0}$ = forced expiratory volume in one sec.

MMMEF = maximum mid-expiratory flow

Recommendations: Prior to an approval letter:

1. Provide from investigator the data from the pulmonary function laboratory used to calculate the results presented in the published report and results shown in the computer print-out. Explain the calculations. Explain any and all discrepancies between the two sets of results. For example, the published report mentions dyspnea in two asthmatic subjects with 46% and 25% reducton in $FEV_{1.0}$ and 39% and 32% reduction in MMEF. Only one of these four values appears in the computer print-out.

2. Provide a list of all possible adverse reactions for all subjects (such as subject "chest sore"). Indicate investigator's judgment that the event was definitely, probably, or possibly related to ribavirin or placebo aerosol.

3. Provide missing data on normal subjects.

4. Provide missing lung volume data.

5. Provide case report forms for all subjects.

6. Provide a justification, if one exists, for use of a treatment which had a significant adverse effect on pulmonary function tests in all COPD subjects and the majority of asthmatic subjects. If no justification is possible, discuss how ribavirin indications should be rewritten.

In addition, the labelling should contain a warning that ribavirin aerosol use has been associated with deteriorating lung function and dyspnea in adults with asthma or COPD.

Hall Pulmonary Function* Study:

This submission was in response to a request for investigator's data from individual subjects. None was available.

The study was a controlled double-blind study in young adults (JAMA 249:2666, 1983). Pulmonary function was evaluated before, during, and after experimental RSV infection. Subjects received either ribavirin or placebo aerosol for 12 h/day for 3 days.

FVC dropped from 13-21% during placebo treatment in 3 subjects. MMEFR dropped from 19-26% after placebo treatment in 3 subjects and 16% after ribavirin in one subject.

The data summary shows mean MMEFR was 10%-12% less during ribavirin treatment than during placebo treatment. The two treatment groups had similar means for FVC and FEV, before, during, and after treatment. Mean FVC, FEV, and MMEFR within each group did not change from day 1 to day 5 to day 60.

*FVC = Forced vital capacity, FEV = Forced expiratory volume in 1 sec, MMEFR = maximal midexpiratory flow rate.

Conclusion: Aerosol treatment (ribavirin or placebo) may produce decreases in pulmonary function in certain individuals. This possible effect should enter into the risk/benefit consideration regarding aerosol use (with or without ribavirin).

Recommendation: The labelling should contain a warning that aerosol use (with or without ribavirin) has adversely affected pulmonary function in normal adults, as well as those with asthma or COPD.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA 5-7-85
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/25/85
3793b

Medical Officer's Review (#13) of NDA 18-859

April 25, 1985

Amendment (56)

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug Ribavirin Aerosol

This submission is in response to my request for information concerning side effects and/or adverse reactions encountered with ribavirin aerosol. Data are referred to from the following previous submissions:

Hall, young adult volunteers, RSV
Hall I, RSV
Hall II, RSV
Taber, 1982-3, RSV
Taber, 1984, RSV
McIntosh, RSV, 1983-4, RSV
Parrott, RSV
Edelsor RSV
Knight, 1980
Knight, 1981
Knight, 1982
Knight 1982
Knight 1983
Compassionate cases

In addition, data are included from a study of ribavirin versus saline aerosol for treatment of bronchiolitis in infants carried out in UK by Barry (King's College Hospital, London) and Cockburn (Royal Hospital for Sick Children, Glasgow). Case report forms for this study were not submitted.

Adverse Reactions and Side Effects:

Anorexia, vomiting, diarrhea, rash, and conjunctivitis occurred frequently, but were often present before treatment and were no more frequent in ribavirin than in control subjects. Cyanosis, apnea, or persistent wheezing were noted infrequently in both groups.

The following events were noted only among control subjects: Respiratory deterioration (2), seizure probably due to hypoxia (1), mucous plugs (1), dyspnea (1), or hyperinflation (1). Only ribavirin recipients (5) experienced drug precipitation, increased PEEP, or other problems with ventilator function. Among compassionate use cases, one ribavirin recipient required prolonged high ventilator settings with emphysema and hyperinflation and one experienced cariac arrest and hypoxia.

Deaths were tabulated only for compassionate use cases. There were four deaths during and eight after ribavirin administration among 86 compassionate cases.

Conclusions:

1. Some placebo recipients experienced deterioration of their RSV infection, in contrast to ribavirin recipients.

2. When used with a ventilator, ribavirin may precipitate, or be associated with increased PEEP, prolonged high ventilator settings, or ventilator malfunction.

3. No adverse reactions were reported other than the difficulties with ventilator use noted above. However, the information previously requested in MOR (#5) has not been provided. Moreover, several adverse events which I have noted in MOR #5 and MOR #10 have still not been acknowledged. No forms 1639 have been sumbmitted. The safety update is incomplete and unsatisfactory.

Recommendations:

1. Before an approvable letter, provide remainder of adverse reaction data including that listed in MOR (#5) item 6 and MOR #10 for all subjects. Form 1639 is to be submitted as well.

2. Restrict use of ribavirin aerosol to subjects not requiring a ventilator until data are submitted that show that problems noted have been satisfactorily addressed. Meanwhile, consider ribavirin for compassionate use for subjects on ventilators. This could be added to the compassionate use protocol.

Barry and Cockburn: RSV Infection in Children in UK.

This randomized, double-blind study included 14 subjects receiving ribavirin and 12 receiving placebo. Analysis of RSV positive subjects indicated significantly more rapid improvement and/or normalization of nasal flaring, chest retractions, crepitations, feeding behavior, and/or attitude. The median duration of RSV shedding was not significantly different in the two groups. No adverse effects were reported.

Conclusion:

1. If case report forms are submitted and agree with the summarized data, this study would represent a third well-controlled study to support the sponsor's claim that ribavirin is effective and safe for RSV lower respiratory tract infection.

2. The lack of virologic effect in this study may be due to the method of determining virus. Nasal secretions (wash or swab not specified) were not titered. The studies where virologic efficacy was demonstrated used more sensitive techniques (viral titration or ELISA).

Recommendations

Prior to an approvable letter, submit case report forms from UK study. Provide information on how nasal secretions were collected (swab or wash).

Victoria Schauf

Victoria Schauf, M.D.

Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/25/85
3845b

Knight

Medical Officer's Review (#12) of NDA 18-859

April 25, 1985

Amendment (59)

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug Ribavirin aerosol

This submission is addressed to safety information regarding SPAG-2 use in ventilated patients. It is dated 4-22-85 and in response to my comments conveyed by telephone. The sponsor had not seen Dr. Tabor's letter dated 4-22-85. The submission does not address many of these previously noted deficiencies.

Table I is a listing of compassionate cases showing difficulties encountered using SPAG-2 in five ventilated patients. Difficulties included: crystalization of drug "in the respiratory system", increase $F_iO_2$ to 100% due to "mechanical problems", worsening of radiologic changes with prolonged high pressure and $O_2$ requirements, drug crystalization, and increased PEEP.

Table II is a telephone survey of eight hospitals concerning precipitation of drug and condensation of water when SPAG-2 is used with a ventilator. Reports note crystalization within the endotracheal tubes and breathing circuit and increase in PIP resulting from crystalization.

Table III is a telephone survey of six hospitals concerning frequency of filter change, which was from 2-24 hours. Table IV is a telephone survey on type and frequency of change of one-way valve. Disposable or reusable valves were checked or changed every 2 to 24 hours.

Appendix I consists of SPAG-ventilator data collected retrospectively from eight subjects receiving the drug on a compassionate basis in 1985. The space on the data collection forms is too small for entry of "reasons patient withdrawn from treatment", "adverse reactions", and "observations" (e.g. see p 32). Many entries are not legible. They should be typed or printed legibly and carefully xeroxed. Deficiencies noted in MOR #9 have not been addressed.

The first report in appendix I, (p 16-21), represents another unreported adverse experience. While receiving digoxin and ribavirin aerosol, the subject developed cardiac arrhythmias, cardiac arrest, and death. Prior to death, he required maximum ventilator settings. Drug precipitates were noted in the ventilator despite frequent filter changes.

The second report (p 22) does not identify the hospital or the subject's diagnosis. Drug crystalization was noted again. PEEP was increased.

The third report (p 24) lacks subject's diagnosis or any narrative report. Drug crystalization noted in tubing to one way valve.

The fourth report (p 27) lacks hospital name, subject's diagnosis, investigator narrative. A seizure is attributed to "hypoglycemic alkalosis", an unusual diagnosis.

The fifth report (p 30) is incomplete and illegible.

The sixth report cannot be read completely because space was not adequate. However, drying chamber had to be turned off per advice from Viratek. Patient was withdrawn from treatment due to wheezing and respiratory distress. No adverse reaction was noted or reported to FDA. SPAG-2 apparently interfered with function of servo volume ventilator and patient had to be switched to pressure ventilator. Drug precipitation resulted in increased suctioning requirement. Staff believed crystals might have been related to patient's respiratory distress.

The seventh and eighth report (p 34) come from Baylor. No patient information is included. No problems were noted with the SPAG-2.

A revised SPAG-2 manual has been submitted with a warning that drug precipitation occurs and that the breathing circuit should be "routinely monitored." This warning is incomplete and does not reflect the necessity of stopping treatment because of or risk to the patient from increased PEEP, PIP, or problems with ventilator function. Items 1-6 and 8-29 in Dr. Tabor's letter of 4-22-85 still require a satisfactory response.

Conclusions:

Numerous problems with the use of SPAG-2, ribavirin, and a ventilator exist. These have not been properly reported to FDA despite numerous requests. These include: crystalization of the drug in the ventilator, breathing circuit, endotracheal tube, and in one case according to the sponsor, even in the patient. Clearly, "blinded" observers in clinical trials were not blind if they observed these crystals. Associated with reports of crystalization have been clinical and radiographic deterioration, requirements for higher ventilator settings, increased PEEP and PIP.

It is not sufficient to say that the crystals may be removed by frequent suctioning. Too frequent suctioning may be traumatic and may influence adversely intracranial pressure and other functions.

Two patients receiving digoxin and ribavirin died. One definitely had arrhythmias. This may have been co-incidental, but raises again the issue that no drug interactions have been studied. Since digoxin, aminophylline, other bronchodilators, and antibiotics will be used frequently in patients receiving ribavirin, studies should be started to determine if physical chemical or pharmacologic interactions are to be expected. In ongoing clinical use, all case report forms should include all concomitant medications.

Recommendations:

1. Prior to an approvable letter, address all deficiencies in Dr. Tabor's letter of 4-22-85 and those noted in MORs as requiring resolution before an approvable letter.

2. Both ribavirin labelling and SPAG-2 manual must report and address the problems which are being encountered with drug crystalization and must clearly state how to avoid the problem or cope with it if it occurs. Similarly, adverse reactions must be clearly stated in both places.

3. Explain how "blind" trials could be blind when drug crystalization seems to occur so frequently.

4. Study physical-chemical and pharmacologic interactions of ribavirin with digoxin, aminophylline, other bronchodilators, and antibiotics after considering protocols with Dr. Brauer.

5. Record all concomitant medications for all subjects on case report forms. Include compassionate use cases.

6. Telephone surveys will not suffice to obtain information as to how often filters should be obtained (Table III). That information is to be obtained by the sponsor or investigator collecting data on SPAG-2 and ventilator performance as a function of timing of filter change. The same considerations apply to the other telephone surveys performed by the sponsor.

7. Information on adverse reactions and problems with SPAG-2 is scattered through the NDA. After most deficiencies have been addressed, this information should be summarized in one place.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ET 5/22/85
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/16/85
3846b

CSO / May 85

Knight

Medical Officer's Review (#12) of NDA 18-859

April 25, 1985

Amendment (59)

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, CA 92626

Name of Drug Ribavirin aerosol

This submission is addressed to safety information regarding SPAG-2 use in ventilated patients. It is dated 4-22-85 and in response to my comments conveyed by telephone. The sponsor had not seen Dr. Tabor's letter dated 4-22-85. The submission does not address many of these previously noted deficiencies.

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Appendix I consists of SPAG-ventilator data collected retrospectively from eight subjects receiving the drug on a compassionate basis in 1985. The space on the data collection forms is too small for entry of "reasons patient withdrawn from treatment", "adverse reactions", and "observations" (e.g. see p 32). Many entries are not legible. They should be typed or printed legibly and carefully xeroxed. Deficiencies noted in MOR #9 have not been addressed.

The first report in appendix I, (p 16-21), represents another unreported adverse experience. While receiving digoxin and ribavirin aerosol, the subject developed cardiac arrhythmias, cardiac arrest, and death. Prior to death, he required maximum ventilator settings. Drug precipitates were noted in the ventilator despite frequent filter changes.

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A revised SPAG-2 manual has been submitted with a warning that drug precipitation occurs and that the breathing circuit should be "routinely monitored." This warning is incomplete and does not reflect the necessity of stopping treatment because of or risk to the patient from increased PEEP, PIP, or problems with ventilator function. Items 1-6 and 8-29 in Dr. Tabor's letter of 4-22-85 still require a satisfactory response.

Conclusions:

Numerous problems with the use of SPAG-2, ribavirin, and a ventilator exist. These have not been properly reported to FDA despite numerous requests. These include: crystalization of the drug in the ventilator, breathing circuit, endotracheal tube, and in one case according to the sponsor, even in the patient. Clearly, "blinded" observers in clinical trials were not blind if they observed these crystals. Associated with reports of crystalization have been clinical and radiographic deterioration, requirements for higher ventilator settings, increased PEEP and PIP.

It is not sufficient to say that the crystals may be removed by frequent suctioning. Too frequent suctioning may be traumatic and may influence adversely intracranial pressure and other functions.

Two patients receiving digoxin and ribavirin died. One definitely had arrhythmias. This may have been co-incidental, but raises again the issue that no drug interactions have been studied. Since digoxin, aminophylline, other bronchodilators, and antibiotics will be used frequently in patients receiving ribavirin, studies should be started to determine if physical chemical or pharmacologic interactions are to be expected. In ongoing clinical use, all case report forms should include all concomitant medications.

Recommendations:

1. Prior to an approvable letter, address all deficiencies in Dr. Tabor's letter of 4-22-85 and those noted in MORs as requiring resolution before an approvable letter.

2. Both ribavirin labelling and SPAG-2 manual must report and address the problems which are being encountered with drug crystalization and must clearly state how to avoid the problem or cope with it if it occurs. Similarly, adverse reactions must be clearly stated in both places.

3. Explain how "blind" trials could be blind when drug crystalization seems to occur so frequently.

4. Study physical-chemical and pharmacologic interactions of ribavirin with digoxin, aminophylline, other bronchodilators, and antibiotics after considering protocols with Dr. Browder.

5. Record all concomitant medications for all subjects on case report forms. Include compassionate use cases.

6. Telephone surveys will not suffice to obtain information as to how often filters should be obtained (Table III). That information is to be obtained by the sponsor or investigator collecting data on SPAG-2 and ventilator performance as a function of timing of filter change. The same considerations apply to the other telephone surveys performed by the sponsor.

7. Information on adverse reactions and problems with SPAG-2 is scattered through the NDA. After most deficiencies have been addressed, this information should be summarized in one place.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/4/16/85
3846b

Medical Officer's Review (#13) of NDA 18-859

July 8, 1985

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, California 92626

Name of Drug: Ribavirin aerosol

Amendment 61

This submission consists of a revised SPAG-2 manual and responses to questions in Dr. Tabor's letter received April 25, 1985.

Questions 1-5, - 8 responses are satisfactory.

Question 7 - No figures have been submitted in this draft.

Question 9 - The answer is only partially responsive and misleading. The use of the drying chamber does influence the aerosol produced. No explanation or data are given as to how changing the aerosol properties will affect the patient. In fact, making the particle larger will probably decrease bioavailability. This deficiency requires immediate resolution if investigational use with ventilators is to continue.

Question 10 - The response is unsatisfactory. It implies that a patient requiring rapid ventilation should not receive it in order that ribavirin therapy can be used.

Question 11 - The response is unsatisfactory and contradictory. Condensation does occur as noted on p 7 SPAG-2 manual.

Question 12.9 - It is stated that "therapists and physicians complained that they could not follow instructions as written." Can they now?

12.11 - What experience? Why is one method "more appropriate."

Question 13 - The data in Amendment (59) are not sufficient to justify ventilator use. All reference to ventilator use should be removed from the manual. A boxed warning statement should be added to the manual stating that concomittant use of SPAG-2 and ventilator are contraindicated because of risk of increased PIP, PEEP, and pneumothorax and because overall safety and efficacy have not been determined. A separate SPAG-2 addendum could be prepared for investigational use with ventilations.

Questions 14-17- Responses are satisfactory.

Question 18 - The answer is nonresponsive. The question "how often?" is not answered. From the data presented, the solution should be replaced every 8-12 hours to provide consistent aerosol characteristics. If this is so, manual and labelling must be revised accordingly.

Question 19 - Modify SPAG-2 units so that flow meters have automatic stops, or justify why this should not be done.

Question 20 - Apparently flow at 12.5 vs 15 L/min changes the output performance of SPAG-2. Indicate how these changes effect bioavailability of drug as originally requested.

Question 21 - The answer is unresponsive. What does a therapist's "preference" have to do with operation of SPAG-2. See also Q 13 above.

Question 22 - The questions were not answered. The data provided is not pertinent to the questions. What is the meaning of Note 1? What is the affect of 2 gm ribavirin precipitate on ventilator performance?

Question 23 - Justify lack of sterility for this valve and any other non-sterile components in patient breathing circuit.

Question 24 - For investigator's brochure, add to Q. that it will be necessary to stop ribavirin/SPAG-2 and provide a breathing mixture from another source while changing filters.

Question 25-29 - Responses are satisfactory.

SPAG-2 Manual Revised May 2, 1985.

Please submit the figures referred to in this draft.

Remove all references to ventilators, including those on p 1, 2, 4 and add a warning as indicated above, Q13.

Page 1. Is non-vented face mask intended? If so, specify.

The meaning of the last sentence is not clear.

Indicate how long aerosol tubing should be. Indicate sterility (or justify use of non-sterile tubing). Indicate how often tubing is to be changed, whether or not it is reuseable, and where to get it.

Page 2. Top "Bacterial" filter is the correct term, not "bacteria" filter.

Page 2. C. Part 3. Does this mean that a clogged nebulizer will give an inaccurate flow? If so, indicate this and add a warning in the appropriate part of the manual. Indicate how often nebulizer is to be monitored for clogging.

Page 3. Note. Also include this note in pertinent part of section G.

Page 3 D. Indicate which, if any, parts in the patient breathing circuit are not sterile. Justify.

Page 3 E. Final wording should agree with final draft labelling. Page number for package insert should be given.

Page 4 F. 3. What is the meaning of "loosely tighten"?

Page 6. Note. Indicate what this frequency should be.

Page 6, 14. Is the mask vented or not? Specify and explain choice.

Page 6, 16. Indicate that gas source may be turned off after assuring that patient has an alternative gas source provided.

Page 6--7 H Remove this section. In preparing materials for investigational subjects on ventilators, in the warnings indicate that when the aerosol is disconnected from the patient breathing source, an alternative gas source must be provided. Also indicate in the warning that if PEEP or PIP are increased by use of ribavirin aerosol that this increase may result in pneumothorax.
Explain 1st note, page 7.
5. "Bacterial" filter not "bacteria" filter.
6. See Q10 above.

Page 8 I Indicate minimum frequency for cleaning.

Amendment (67)

This lengthy submission consists of a compilation and summary of some ribavirin aerosol side effects. The 14 deaths noted in Amendment (75) are not mentioned in this summary. No information is included about laboratory parameters of safety (e.g. hematology, chemistry).

Pages 1-181 are xeroxes of Amendment (56 pages 1-181.) This material was reviewed in MOR (#11.)

The remainder of the submission is composed of xeroxed pages from Amendment (55). These pages are out of order, but otherwise nothing new is included. This material was reviewed in MOR (#10).

Conclusion and Recommendations: As noted in MORs (10 and 11). A satisfactory compilation of safety data is still required.

Amendment (75)

This lengthy submission is in response to our request for autopsy data on all subjects who died during or after ribavirin aerosol. This data was requested by Dr. Esber in order to determine possible pulmonary toxicity of ribavirin aerosol. Fourteen of 83 compassionate use subjects died. Histopathology was presented from two subjects. One lung biopsy revealed mononuclear and mutinucleate cells in alveoli and fibrinoid precipitate in alveoli; bronchioles revealed squamous metaplasia. Findings were consistent with "virus infection". One post-mortem study revealed acute and chronic infiltration by lymphocyte, PMNs, and histocytes; proliferation of respiratory epithelium, edema of alveoli, giant cells; all consistent with RSV pneumonia. Additionally, there were superimposed acute bronchopneumonia and abscess formation with necrotizing vasculitis and large hemorrhages. Electron microscopic studies were performed, but results were not submitted.

Conclusion:

1) The sponsor did not take the trouble to request autopsy reports where none were submitted. Provisional (gross) autopsy reports were not followed by histologic reports.

2) The changes noted above in the presence of infection cannot be attributed solely to ribavirin; however, ribavirin may have been a co-factor in eliciting hemorrhage, edema, inflammation, and metaplasia. Similar changes have been reported in uninfected animals treated with ribavirin aerosol.

Recommendations

1. Submit final autopsy reports for all subjects (including those in controlled trials) who underwent autopsy. So far only one final report has been submitted.

2. Include any lung biopsy reports during or after ribavirin aerosol. (E.G. compassionate case no. 9.)

3. Include EM results when the studies were performed. (E. G. compassionate case nos. 28, 58.)

4. Follow-up to see if subjects with severe underlying disease died after investigator's reports to Viratek. In these cases, provide histopathology reports from final autopsy report.

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This submission consists of responses to questions of Dr. Browder conveyed on 7-2-85.

Question 1 is another request for information on interactions of ribavirin with digoxin, aminophyllin, other bronchodilators, and antibiotics. No data were submitted.

Question 2 is a request for pharmacologic data. No new human data were submitted. The conclusion that intracellular ribavirin concentration cannot be less than plasma is not warranted from the data shown. However, the conclusion may to correct. (Data to support the statement that the plasma half-life of ribavirin is "longer than previously reported" is not explained or supported by the data shown. Similarly, the statements concerning respiratory secretions are unsupported.)

The clinical pharmacokinetic summary is not in a format to be verified from the data submitted to the NDA.

Please see Dr. Browder's review of animal data.

Question 3 is a request for data to support the claim that pulmonary lesions in ferrets are "spontaneous" rather than ribavirin induced. No data to support this claim were submitted.

Conclusions and Recommendations:

The entire submission is non-responsive. Prior to an approvable letter, the sponsor should prepare protocols, identify investigators, and commit funds to resolving Questions 1 and 2 to the satisfaction of the pharmacology reviewer.

The ribavirin associated pulmonary lesions in ferrets cannot be attributed by the sponsor to "spontaneous" disease on the basis of this submission.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-340
HFN-815
HFN-815/CSO
HFN-815/VSchauf:bam:7/11/85
0054m

for E.T. 29 July 85

Medical Officer's Review (#13) of NDA 18-859

July 8, 1985

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, California 92626

Name of Drug: Ribavirin aerosol

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SPAG-2 Manual Revised May 2, 1985.

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Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-340
HFN-815
HFN-815/CSO
HFN-815/VSchauf:bam:7/11/85
0054m

for E.T. 29 July 85

MEDICAL OFFICER'S REVIEW (#14) OF NDA 18-859

Sponsor: Viratek

Drug: Ribavirin aerosol

This submission consists of a draft which the sponsor dubs the "final" package insert.

Page 2. The headings "antiviral effects," "immunologic effects," "microbiology" and "pharmacokinetics" should all be in the same format. Immunologic is misspelled in paragraph 3 of Clinical Pharmacology.

Page 3. Para. 5. Last sentence. Remove "had peaks ranging."

Page 5. Contraindications. 1st sentence. Insert "severe" before "lower respiratory tract infection." A paragraph should be added as follows:

> "Ribavirin aerosol should not be used for infants requiring assisted ventilation because precipitation of the drug in the respiratory equipment may interfere with safe and effective ventilation of the patient."

Pages 5 & 6. Under "Warnings" and in the boxed Warning add a paragraph stating that: "Ribavirin administration produced cardiac lesions in rats, mice, and monkeys. Ribavirin aerosol administration resulted in inflammatory, proliferative, and possibly emphysematous changes in the lungs of developing ferrets. The significance of these findings to human administration is unknown."

Page 6. Warnings. As discussed in the labelling meeting on 6-17-85, the warnings should also contain the statement that:

> "Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic. Ribavirin has not been evaluated in human pregnancy. However, results of animal studies suggest that teratogenic effects may occur (see contraindications)."

The Divisional Director at the labelling meeting of 6-17-85 did not concur that this statement from the boxed warning should also be in Warnings.

Page 6. Drug interactions. Insert "antibiotics" after "other antiviral agents." Last word substitute "evaluated" for "described."

Page 7. Adverse Reactions. Para. 1. Insert after first sentence the following:

> "Dyspnea and chest soreness were also reported in the latter group."

Page 7. Adverse reactions. Para. 1. Last line should begin a new paragraph and should be revised to read:"...respiratory tract disease. Reticulocytosis has been observed in infants, but the frequency is not known."

Page 7. Adverse Reactions Para. 2 should be revised to state that:

> "Anemia, which occurs frequently with oral and intravenous ribavirin, has not been shown to result from use of the aerosol. A single infant receiving ribavirin aerosol experienced a 25% reduction in hematocrit. However, most infants have not been evaluated at the time after treatment when anemia is most likely to occur, namely 1-2 weeks post-treatment."

Adverse Reactions Para. 3. The following should be added:

> "In a group of severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation, the following were rarely associated with ribavirin aerosol use: bacterial pneumonia, pneumothorax, digitalis toxicity, hypotension, cardiac arrest, apnea, worsening of respiratory status, respirator dependency, and/or death.
>
> "In some subjects requiring assisted ventilation, ribavirin aerosol has caused difficulties in providing adequate ventilation to the patient due to precipitation of drug within ventilatory apparatus including the endotracheal tube, increase positive end expiratory pressure, increase positive inspiratory pressure, and accumulation of fluid in tubing ("rain out"). These problems may seriously jeopardize gas exchange."

Page 8. Para. 4. In view of the new data submitted by Viratek showing that the aerosol properties change after 10 hours aerosolization, these materials should be revised to require a new solution be prepared and placed in a new flask at least every 10-12 hours.

Page 9. Last sentence. This sentence should also appear, prominently displayed, in "Dosage and Administration."

Ref. 1. Remove the 1 before 1980.

Note: The attached draft review from Biopharmaceutics also contains recommendations for labelling revision with which I concur. I suggest these be transmitted to the sponsor.

Victoria Schauf

Victoria Schauf, M.D.

cc: Orig NDA
HFN-815 ~~8/22/85~~
HFN-340
HFN-815/JKnight
HFN-815/VSchauf:mas-8/1/85-0020d

Ribavirin ✓ Drafts

III. OVERALL DEFICIENCIES

1. You, as the sponsor, have provided summary results for eight studies that were carried out in different aged patients (infant to adult) using different doses by different routes of administration. Most of those studies were carried out such that the drug was not according to the recommended dosage and administration (i.e., treatment for 12-18 hours per day for at least three and no more than seven days) of the labeling section. These studies, as a whole, are deficient in that:

   a. the studies can only be considered as pilot studies due to the small number of patients (i.e., 2 to 4 subjects) enrolled per study,

   b. no assay validation data were provided per study,

   c. incomplete demographic data were provided,

   d. only minimal tabular data (i.e. plasma profiles) were provided, and

   e. the method of calculating drug's half-life was not described;

2. Some studies' results to support certain statements of your labeling in the 'Pharmacokinetics' Section (e.g., metabolism and excretion) were not provided. The firm should provide information/data to support those labeling statements or retract it from the labeling.

IV. COMMENTS

1. You should modify your drug labeling to incorporate more specific information (e.g., number and types of age groups, diseased states, how and how much for how long drug doses were given, etc.) and exclude study data obtained from aerosol therapy with assisted respirator (endotracheal tube) since this method of aerosol administration is not being prescribed and data obtained by it may be misleading for the prescribed procedures. For examples, the label may be stated as:

   . "Following oral dosing of 1000 mg/day given in three divided doses for 10 days in four ADULT patients, plasma ribavirin concentration ranged 1.7-5.3 uM after 2.5 hours with a mean concentration of 3.1 uM."

   . "Four PEDIATRIC patients inhaling ribavirin aerosols administered by face mask for 2.5 hr each day for three days had plasma concentration range of 0.44-1.5 uM at 2.5-hr postdose with a mean concentration of 0.76 uM." The plasma half-life was reported to be 9.5 hr.

   . ETC. (continued as for other doses).

   . " X pediatric patients were given ribavirin aerosols therapy by (face mask, mist tent, air hood) for Y hr each day for Z days, plasma concentrations range was shown between U uM and V uM after W hr with mean concentration of ___ hr. and wwith plasma half-life of A hours."

2. You should include the following type statements in your labeling under the Pharmacokinetic Section until such time accurate information is available.

. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

V. RECOMMENDATION

The NDA 18-859 submissions, which were filed both on June 18, 1985 and on November 4, 1983 by Viratek, are approvable by the Division of Biopharmaceutics for inhalation therapy in that the in-vivo bioavailability/bioequivalent (BA/BE) requirement can be DEFERRED under Section 21 CFR 320.22 (e) of Agency's BA/BE requirements (i.e. for good cause). However, the firm should agree in writing to conduct a well-controlled study(ies) to better define this drug's inhalation pharmacokinetics in the intended patient populations in order to support the drug's labeling. It is recommended that the firm consult with the Division of Biopharmaceutics to discuss the protocol(s) for such a study(ies) prior to initiation. The overall deficiencies #1 and 2, comments #1 and 2, plus this recommendation should be communicated to the firm.

T.E. Mary Ong-Chen, Biochemist
Pharmacokinetic Evaluation Branch

RD Initialed by John P. Hunt
FT Initialed by C.T. Vishwanathan, Ph.D. _____

cc: NDA 18-859 Orig.; HFN-225 (Chen); Chron, Division, Drug & Review Files.

TOC:smj:dea:4455x(07/02/85)

Medical Officer's Review # 15 NDA 18-859

September 10, 1985

Amendment 79

Sponsor: Viratek

Drug: Ribavirin aerosol

Related Review: MOR # 13, Amendment (75).

This submission consists of responses to requests for information about autopsies. Final autopsy reports were requested. Autopsy reports were submitted as follows:

Compassionate Case 9

SCID
Interstitial pneumonia
Bilateral pneumothoraces
Pulmonary alveolar proteinosis
Pleural adhesions

Compassionate Case 24

Trisomy 21.

Congenital heart disease
Congenital sublobar emphysema

Microscopic: emphysema RUL
patchy bronchopneumonia
hyaline membranes
subpleural hemorrhages

Compassionate Case 28

Combined variable immunodeficiency
S/P bone marrow transplant
Pneumonitis with abscess formation, possibly viral

No microscopic data from autopsy. A lung biopsy five days prior to death showed alveoli filled with mononuclear cells and fibrinoid material.

Compassionate Case 58

Severe interstitial pneumonitis (RSV) with edema, fibrin plugs, hyaline membranes, and mononuclear cell infiltrate.
Pneumopericardium
Pneumothorax
Pulmonary adhesions

Compassionate Case 62.

Previously, reported as dead; now claimed to be alive.

Conclusion and Recommendations

The pathological materials are very limited. Some changes, including inflammatory infiltrates, pneumothorax, pneumomediastinum, pulmonary hemorrhages, fibrinoid deposits or plugs, hyaline membranes, and metaplasia are consistent with the underlying viral pneumonia or its standard treatment. However, the possibility that ribavirin may have contributed to these changes cannot be eliminated with the information available at this time. In addition, alveolar proteinosis is an unusual finding. This diagnosis is based on PAS positivity of alveolar material. It may be that ribavirin deposits would be PAS positive. The autopsy findings are inconclusive with respect to identifying pulmonary toxicity definitely attributable to ribavirin aerosol. Prospectively designed pre-clinical and clinical studies are more likely to be revealing, and these have been addressed in previous reviews.

Amendment 81, Vol I and II

This submission consists of adverse drug experience reports collected retrospectively from Drs. Hall, Taber, McIntosh, Rodriequez, Edelson, and Knight. Numerous reversible events occurred in both placebo and ribavirin recipients probably due to the underlying infection. Reports were submitted on placebo recipients even though ribavirin could not possibly have been implicated. However, conjunctivitis was reported in five placebo and 16 ribavirin recipients (no denominator provided).

Several adverse experienced noted in other reviews were omitted (e.g. anemia, reticulocytosis, decreased pulmonary function, pneumothorax, drug precipitation with ventilator, increased PEEP, death). No compassionate cases were included in this submission, and is hard to imagine 86 sick babies with no adverse experiences. The adverse experiences noted by Light and Aoki (MOR 10) were also excluded.

Conclusions and Recommendations

. Prior to an approvable letter, the firm should:

1. Address labelling deficiencies noted in MOR #14.
2. Summarize all adverse experience and address deficiencies noted in MOR's 5, 10, and 11.
3. Commit to providing adequate monitoring and reporting of all adverse experiences. Demonstrate that this committment can be met with current staff.

NDA 18-859

Amendment 81, Volume III

This submission relates to the potential problem of dilutional hyponatremia/water intoxication from aersol use and consists of a testimonial letter from Dr. McBride, a consultant to the firm. Although Dr. McBride "feels strongly that water intoxication need not be a concern," no data are presented. This problem was discussed with the sponsor and Dr. McBride (See Memorandum of Meeting 7/24/85). At that time, it was agreed that this data could and would be provided.

Conclusions and Recommendations

Prior to an approvable letter submit prospectively or retrospectively collected data on weight, serum sodium, or any appropriate variable before, during, and after ribavirin or placebo aerosol treatment. These data are required in case the rationale leading to Dr. McBride's feeling is incomplete or incorrect due to factors unforeseen by Dr. McBride.

Amendment 60

This submission consists of additional safety information concerning SPAG-2 in ventilated patients. This data was collected retrospectively using a poorly designed data collection form (See MOR 9 & 12). There were five ribavirin and three placebo cases from Dr. McIntosh and one case each from Columbus Children's Hospital and the University of California Irvine Medical Center.

Dr. McIntosh reported the following:

Ribavirin (SPAG-2 drying chamber on):

"Crusting in exhalation valve" requiring temporary withdrawal from treatment. Treatment discontinued at death of child from severe combined immunodeficiency disease and refractory RSV infection.

"Baby very agitated; tubing plugged with drug."

Hypoxia at time expiratory valve cleaned.

Control

Required reintubation.
Required reintubation.

Columbus Children's Hospital:

Patient withdrawn from treatment because of atelectasis.

UCIMC

Investigator's "impression was that increased tracheal secretions and shifting atelectasis may have been 2° to aerosol therapy. However, tracheal secretions continued p therapy was discontinued" and may have been due to other causes.

Conclusions:

As noted in MOR (#12) and other reviews, there remain very serious concerns about the safety of using SPAG-2 and ribavirin in conjunction with a ventilator.

Recommendations:

1. Use with a ventilator should be restricted to with well qualified investigators who are aware of the numerous adverse experiences noted in this and other reviews and who are prepared to monitor use closely and to deal with adverse events as they arise.

2. A protocol should be submitted to investigate IV use as a potentially safer route when a ventilator is required.

3. The adverse experiences noted in Amendments 59 and 60 should be reported on forms 1639 and be included in any summary of adverse experiences for the NDA and for

Amendment (82)

This submission consists of a revised SPAG-2 manual which excludes reference to use with ventilated patients.

Recommendations:

The sponsor should be advised also to address all deficiencies noted in MOR (#13) and revise accordingly prior to my third review of the manual.

Note: Ms. Hunter in Devices HFZ-430 will be forwarding her comments regarding use of SPAG-2 this week.

Victoria Schauf

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ST 9/20/85
HFN-815/CSO
HFN-340
HFN-815/VSchauf:llm/9/5/85
0198m

LRD 12Sep85

Medical Officer's Review #16 Ribavirin Aerosol Advertising NDA 18-859

Sponsor: Viratek

This submission was sent to me by Mr. Yellin of HFN-244 and is the "third revision" of the "Product Monograph for Virazole" and is said to be exemplary of the entire promotional material. The proposed material is grossly inaccurate, misleading, and is not in accord with the proposed labeling.

Specific problems are:

1. Claims based on references which should be restricted to peer reviewed articles. For example, the company paid symposia which resulted in non-refereed books should not be cited.

2. Page two has three major inaccuracies. First, immunization programs for influenza have been successful. Second, "prophylactically" is used incorrectly; in the context, "empirically" is the correct word. Third, most virus infections are self-limited. These inaccuracies are grossly misleading, and lead to several dangerous, incorrect conclusions—that virus infections cannot be prevented with vaccines, that they are not ordinarily self-limited, and that prophylactic antiviral treatment would generally be desirable. This material, if corrected, would still be totally irrelevant to the single, very limited indication, for which the drug may be approved. A minor inaccuracy is the use of the term "strains of the common cold." Colds don't have strains.

3. Page 4. The statement "...acyclovir is the first compound to gain clinical acceptance." is false. The term "broad-spectrum" is incorrect, mis-used, and misleading. It refers to the activity of antibiotics, not antivirals, against gram positive and gram negative bacteria. This material, if corrected, would still be totally irrelvant to the single, narrow limited indication for which the drug may be approved.

4. Page 5. The first sentence "Virazole is the only antiviral drug..." is misleading because it is the only antiviral drug to have been tested for the disease and because most of the infants with lower respiratory tract infection need no treatment. The value $p < .001$ for retractions, rales, viral shedding is incorrect and disagrees with the table on page 6. The seven trials were not all adequately controlled and some were not controlled at all. Only two of the seven trials showed efficacy. The statement beginning "of particular relevance" is probably of no relevance. Although the rate of improvement was greater with drug than placebo, the actual values were not significantly different between the groups.

   "The treatment period" is confusing since it apparently refers to the duration of treatment each day not to the duration of the entire course of treatment.

The net effect of these grandiose, inaccurate, incomplete, and misleading materials is to overstate grossly the modest effect which actually has been shown in two (not seven) studies.

The statement "Virus shedding titers..." should be revised to state that no antiviral effect was demonstrated in the Taber study.

5. Page 7. The left-hand figure shows a placebo line which cannot be distinguished from the ribavirin line. Both figures and one on page 9 are marked "position only." What does this mean?

6. Page 9. Reference should be included for Taber. A typographical error from the reference is included and makes no sense "...more rapidly with ribavirin showed more rapid..." The second quote, "...Administration of the drug..." is out of context. Are the sponsors suggesting treatment outside a hospital?

7. Page 10 Paragragh 1. This is not as it will appear in the proposed labelling.
Paragraph 2. This discussion of anemia is out of context for the proposed aersol use. However, if the discussion is be included in this fashion, it is necessary to say that oral administration in man has resulted in profound anemia requiring, in some cases, blood transfusion.
Paragragh 3. This is irrelevant to the proposed use of aerosol.
Paragraph 8. Dr. Shulman's opinion is not properly labelled as opinion. The reference was paid for by the sponsor and has not been peer reviewed. The opinion is not in a relevant context.
Paragragh 9. The potentially severe bronchospastic response to ribavirin in patients with underlying lung disease is not known to be "minor." This is misleading and may cause physicians to monitor patients less intensely than is necessary.

8. Page 11. The entire content of this page fails to conform to the content of the proposed labelling and is inaccurate, false, and misleading.

9. Page 12. The first and second answers are incorrect; the data in the NDA does not support the answer. The answers do not conform to the draft labelling.

The additions to the third answer still do not correct the false impression created by the first sentence.

The fourth answer does not specify that resistance may be detected when many people receive the drug and/or when the drug has been in use for a longer period.

10. Page 13. The first answer is misleading since no advantage has been shown for aerosol versus some other route of treatment. Moreover, the concentration in respiratory secretions does not reflect the intracellular concentration whhich would be the relevant parameter for an intracellular virus, such as RSV.

    The second answer did not come from the listed experts; it came from FDA.

    The third answer is incorrect; in the controlled trials where the drug was effective, hospital stay was not shortened.

    The fourth answer is incorrect; only hospitalized infants with severe lower respiratory disease thought to be due to RSV would be candidates. RSV would need to be documented in the first 24 hours of treatment. Again this material is from labelling; not from the named experts.

11. Page 14 - 15. Mechanisms of action. This section is highly speculative, irrelevant, and not based on data for RSV (the only indication). The implication that viral resistance to RSV will not develop has no basis and cannot be permitted.

12. Page 16-17. Does not conform to or agree with proposed labelling. (All sections, but recommended dosage is worst).

13. Page 18-19. Does not conform with proposed labelling.

Recommendations

1. The above listed problems (1-13) should be corrected and the advertising should conform to the proposed labelling.

2. The firm should commit to responsible, ethical advertising.

3. Marketing of ribavirin aerosol (NDA 18-859) should not be permitted until it is clear that this committment has been made and the problems noted above have been corrected and reviewed.

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-340
HFN-815 ST 1/2/86
HFN-815/CSO
HFN-815/MO
HFN-[redacted]/AKYellin (HFA-244)
HFN-815/VSchauf/llm/12/11/85
0526m

Medical Officer's Review #16 ...avirin Aerosol Advertising NDA 18-859

Sponsor: Viratek

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Specific problems are:

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2. Page two has three major inaccuracies. First, immunization programs for influenza have been successful. Second, "prophylactically" is used incorrectly; in the context, "empirically" is the correct word. Third, most virus infections are self-limited. These inaccuracies are grossly misleading, and lead to several dangerous, incorrect conclusions--that virus infections cannot be prevented with vaccines, that they are not ordinarily self-limited, and that prophylactic antiviral treatment would generally be desirable. This material, if corrected, would still be totally irrelevant to the single, very limited indication, for which the drug may be approved. A minor inaccuracy is the use of the term "strains of the common cold." Colds don't have strains.

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13. Page 18-19. Does not conform with proposed labelling.

Recommendations

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2. The firm should commit to responsible, ethical advertising.

3. Marketing of ribavirin aerosol (NDA 18-859) should not be permitted until it is clear that this committment has been made and the problems noted above have been corrected and reviewed.

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-340
HFN-815 ST 1/2/86
HFN-815/CSO
HFN-815/MO
HFN-[redacted]/AKYellin (HFN-244)
HFN-815/VSchauf/llm/12/11/85
0526m

Medical Officer's Review (#17) of NDA 18-859

December 5, 1985

Sponsor: Viratek
3300 Hyland Avenue
Costa Mesa, California 92626

Name of Drug: Ribavirin aerosol

This submission consists of three protocols, two of which are for studies which the sponsor must commit to perform as a condition for NDA approval. In addition, there is a protocol for evaluation of use with a ventilator. The protocols were previewed by me and this submission contains responses to the items in the FDA letter to the firm dated 9/20/85.

I. Assessment of Environment Exposure to Ribavirin

1. Response 1.a. is unsatisfactory because the subject must have a negative pregnancy test when the study drug is to begin. Since pregnancy may occur after agreement to participate is given, the test must be done when the study drug is to begin.

2. Response 1.b. is unsatisfactory. The subjects included must practice a reliable method of contraception. The exclusion of women who do not use contraception is necessary, but not sufficient.

3. Response 1.c. is satisfactory.

4. Response 1.d. is incomplete. At what temperature will the specimens be stored? How long? How does this affect rivavirin determination?

5. Response 1.e. is in accord with what was requested. However, since the proposed labelling will have 24 hour changes in the reservoir, the sponsor should be requested to revert to the original 24 hour changes which were proposed.

6. Response 1.f. is acceptable.

7. Response 1.g. is nonresponsive, but a response would not be absolutely required.

8. Response 1.h. is satisfactory.

9. Response 1.i. The consent form still does not describe mutagenicity, teratogenicity and carcinogenic potential accurately and in lay terms. The sponsor should use the appropriate section of the forms in to correct the problem.

10. Response 1.j. is incomplete because the information is

to be added to the consent forms.

II. Long Term Follow-up of Infants and Children

1. Response 2. a. is satisfactory.

2. Response 2.b. is incomplete. The sample sizes to achieve statistical significance or to determine the validity of a negative result have not been estimated. The changes which would be considered clinically specific have not been specified. How underlying lung disease would be handled in the analysis has not been specified.

3. Response 2.c. The case report form is not adequate to show results of pulmonary function tests. Nor does it allow space to record previous RSV infection, placebo or rivavirin treatment, or intercurrent infection.

4. Response 2.d. The consent form is unsatisfactory in that it states that subject was treated with ribavirin, when the treatment may have been placebo. The form unnecessarily contains details of acute ribavirin toxicity. These should have been explained in the previous form. The consent form does not indicate as it should that FDA personnel may examine the patient's records.

5. Response 2.e. is unsatisfactory as noted in 2.b. above.

6. Response 2.f. The response simply restates the consideration. Is this now to be incorporated into the protocol?

7. Response 2.g. The disclosure statement is satisfactory.

III. The SPAG-2 Connected to a Ventilator for Administration of Ribavirin Aerosol to Infants with Life-threatening RSV Infections.

1. Response 3.a. Satisfactory.

2. Responses 3.b. and c. are not satisfactory, because the text does not reference the manual (Appendix A) or Appendix B. Many of the SPAG-2/ventilator deficiencies noted in previous and NDA reviews have not been conveyed to the sponsor. Section 6.2.1 will need to be revised when these deficiencies have been conveyed.

3. Response 3.d. is unsatisfactory because the information that suctioning times will be recorded has not been added to the protocol. Appendix A is not referenced in the protocol.

4. Response 3.e., f. Satisfactory.

5. Response 3.g. Unsatisfactory. The form unnecessarily explains

details of acute toxicity of systemic ribavirin. See also I. 9. The trauma of suctioning would not be to the lungs, but to the bronchial tree.

6. Response 3.h. See I. 5. above.

7. Response 3. i. is satisfactory .

8. Background and Rationale Section 1.0 states "the filter should be examined..." This is described in detail in another section; in this section, it is meaningless because which filter is not specified. This and the statements that malfunctioning ventilators should be replaced and that "medical personnel should be notified if patient's lung mechanics change" are self evident, not described in detail enough to be useful, and are out of context in this section. To suggest that adverse reactions are unrelated to drug because of underlying disease is incomplete. The investigator must also consider the possibility that adverse reactions are drug-related.

   Section 2.0. is true but so out of context that it appears to be silly. (This also applies to Protocol II).

   Section 8.2. 4. is absurd. How can a baby on a ventilator "fail to comply with the study evaluation requirements"?

   Section 8.2 provides for reporting adverse reactions related to the device, but not to the drug.

Conclusions:

The protocols are still unsatisfactory and incomplete in many important ways as noted above in detail. In addition, principal investigators have not been designated for any of the studies.

Recommendations:

1. Protocols I and II should be on hold until the deficiencies are corrected and the PIs identified. These items should be corrected prior to an approvable letter for NDA 18-859. The revised protocol should also be submitted to

2. Protocol III. Although ventilator use may proceed on a compassionate basis, the protocol deficiencies should be corrected immediately and a PI designated. The deficiencies include ones from previous reviews have yet to be communicated to the firm. These should be communicated immediately. The protocol should be submitted to

Victoria Schauf, M.D.

cc:
Orig NDA
HFN-815 ~~GT 1/2/86~~
HFN-815/CSO
HFN-340
HFN-815/VSchauf:js/12/10/85
0524m

CHEM
REV

Division of Anti-Infective
Drug Products
Chemist's Review #1
Date Completed: 1/19/83

A.1. NDA 18-859

Applicant: Viratek, Inc.
Covina, CA 91722

2. Product Names:

Proprietary: Virazole

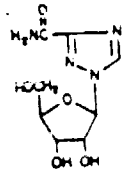
Non-Proprietary: Ribavirin (USAN)

3. Dosage Form & Route of Administration: Aerosol, Inhalation

4. Pharmacological Category and/or Principal Indication:

Anti-viral; for respiratory virus.

5. Structural Formula & Chemical Name:



1H-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl-

B.1. Initial Submission:

Dated: 9/21/82
Received in Bureau: 9/21/82
Received by Chemist: 9/27/82

3. Supporting DMF:

3. Related Documents:(

C. Remarks:

Our letter of October 18, 1982 informed the applicant of our refusal to file application.

D. Conclusion & Recommendation: NDA is not approvable under sections 505(b)(4) and (6) of the Act. See attached "Draft of Chemist's Part, Letter to Applicant."

William F. Kochert

cc: Orig. NDA
HFN-140
HFN-140/CSO
HFN-140/WKochert: gm 1/21/83
HFN-616
R/d Init. by:ARCasola/1/20/83
7365A

SYNTHESIS SCHEME

E. Review Notes:

1. Components: All components are listed.

2. Composition:

| Ingredient | Per vial |
|---|---|
| Ribavirin | 6 grams |

To be reconstituted in 300 ml sterile water to make a 20 mg mg/ml solution and administered using the Small Particle Aerosol Generator.

3. Facilities: The facilities and equipment are described in detail and are satisfactory.

4. Personnel: Qualifications and experience of key personnel are given and are adequate.

5. Synthesis: The synthesis is described in detail with quantities, conditions and yields given. The flow diagram is as follows: (See page 6)

6. Raw material Controls:

(a) New Drug Substance:
Loss on Drying (NMT 0.5%), Appearance of an aqueous solution (clear and colorless), Melting point (165-176°C), IR, TLC (NMT 0.5% of 1-(5'-O-benzoyl-B-D-ribofuranosyl)-1,2,4-triazole-3-carboxami
Assay by HPLC (NLT 98.5%), Purity by UV, Heavy Metals and Arsenic are determined. Specifications and methods are satisfactory.

(b) Other Ingredients: Water for Injection, USP-Tests run are not specified.

7. Other Firms:

8. Manufacturing and Processing:

9. Container:

10. Packaging and Labeling:
Described in detail and is adequate.

11. Laboratory Controls (Finished Dosage Form):
Weight (6.00 gms + 0.60), Water content (NMT 0.05%), TLC, HPLC, UV (Identity and Assay), IR and Sterility (USP XX) are determined. Specifications and methods are satisfactory.

12. Control Numbers:
Control numbers are adequate.

13. Stability:
No data were submitted for the lyophilized powder.

Stability data for the reconstituted solution at 12, 24,48, and 72 hours at 25°C and 35°C indicated a stable product.

14. Samples and Results:
Samples and results were submitted.

15. Labeling:
Container Label: Satisfactory except the type size of the generic name is too small.

Package Insert: Satisfactory

Carton: Satisfactory except the type size of the generic name is too small.

16. Establishment Inspection:
Not requested

17. Registration: The firms are registered.

18. Part 5, Form 356H: Satisfactory.

19. Environmental Impact Analysis Report:
An environmental impact analysis report indicates that an environmental impact statement is not necessary.

"Draft of Chemist's Part, Letter to Applicant"

We have completed our review and find that the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

The application is inadequate under section 505(b)(4) of the Act as follows:

It fails to include a full description of the laboratory procedures that will be employed to check the specifications for the raw material, water for Injection, USP.

It fails to submit stability data for the packaged drug product.

The application is also inadequate under section 505(b)(6) of the Act in that the type size of the generic name of the drug as it appears on the container label and carton is too small. See 21 CFR 201.10.

Division of Anti-Infective
Drug Products
Chemist's Review #2
Date Completed: 10/16/84

A.1. NDA 18-859

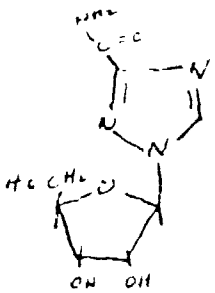
Sponsor: Viratek, Inc.
Covina, CA 91722

2. Product Names: Generic: ribavirin
Proprietary: Virazole

3. Dosage Form & Route of Administration: cryodessicated sterile solid for aerosol inhalation after dilution with sterile water for injection.

4. Pharmacological Category and/or Principal Indication: Treatment of children (no ages stated) with respiratory syncytial virus infections.

5. Structural Formula and Chemical Name(s):



1-B-D-ribofuranosyl-1,2,4 triazole-3-carboxamide

B. 1. Original Submission: 9/12/82. (review #1 1/19/83; WFKochert)

2. Control Amendments: 9/11/84; 9/14/84 (2) 9/17/84, 9/25/84

3. Related Material:

C. Remarks:

The submitted analytical controls are poorly defined and incomplete. Contradictions are apparent in various analytical conditions and equipment (e.g. HPLC column dimensions, flow rates). It is not possible to assess adequacy of the controls without correction of apparent errors and submission of developmental data. The proposed specifications could not be met by the applicant since they fail to incorporate reasonable limits - e.g. words are used such as the peak heights must be "identical", etc.

Since the methods are ill-defined, the stability data are also not amenable to complete analysis.

The sponsor has evidently obtained a new source for the bulk new drug substance, Eastman Kodak. Kodak has not submitted in-process controls. It is therefore not possible to perform a total sequential review of overall controls.

The sponsor is also filing a Medical Device Application in support of their new, revised SPAG-2 aerosol generator (a desk copy of a 510(k) has been provided). A review from Medical Devices should obtained prior to approval. If this indeed a unique aerosol generator and necessary to therapeutic efficacy and safety, the labeling should so state.

The sponsor has also obtained a new manufacturer for dosage form. It is not stated who will now perform final p[illegible] testing.

The sponsor has recommended on previously labeling that the generator be disinfected by nebulizing 70% EtOH. Either Medical Devices or our medical (or microbiological staff) presumably should assess the adequacy of such a procedure and/or the necessity of supplying complete sterilization directions.

D. Conclusions and/or Recommendations:
The application is non-approvable per 505(b)(4) and 505(b)(5) as detailed in the attached chemist's draft.

Establishment inspections are requested with this review.

Methods validation has not been requested since the methods are regarded as incomplete. Validation should be required.

As noted in Remarks, the SPAG-2 generator requires a concurrent review by Medical Devices. The desk copy of the 510(k) should be provided to the reviewing M.O., since it contains "assisted ventilation" procedures.

John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815
HFN-616
1928b

HFN-815/CSO
R/D Init. by: ARCasola 10/16/84

HFN-815/Taylor: gm 10/17/84
ARC 10/23/84

1&2. Components and Composition:
Ribavirin 6000 mg as a lyophilized sterile solid.

3. Facilities:

4. Personnel: Adequately described.

5. Synthesis: A detailed account of the synthetic pathway has been submitted (see item 3). however no analytical controls are provided. In this regard, the raw material specifications, in-process controls, and penultimate precursor characterization require detailed accounts. The synthetic pathway is as follows:

6. Raw Material Controls:
a) Ribavirin — Inadequate.

5

6

7) In this reviewer's opinion the methods will require validation.

8) The sponsor should identify degradation products, if any, produced by acid hydrolysis, and photolysis or at least demonstrate method specificity by assay of stressed samples.

9) Since the drug substance is now produced by (see item 5) utilizing different conditions and controls, the overall adequacy of the methods cannot be totally assessed pending clarification of in-process impurity controls.

10) For additional comments for "revised methods" see item 12.

b) Water for Injection: Per USP. Adequate.

7. Other Facilities: See item 3.
For clarity, the sponsor should withdraw the previous contractors and also state who will perform the final product tests.

8. Manufacturing and Processing:

9.

10. Packaging and Labelling: Satisfactory.

11. Control: (dosage form): (See item 12, addendum).

Weight variation
Appearance
UV assay: 98.5%- 101.5%
HPLC: 98.5% pure by peak height or area
TLC: per active ingredient

Comments: Weight variation should be as per USP XX.
For HPLC, TLC comments see item 12. THe specification fail to include pH or optical rotation. The m.p. apparently from firm's data is in the area of 100°C lower than the raw material.

12. Stability:

Stability Addendum:
Stability data - 9/25/84 submission of 6 volumes

This submission includes revised specifications and methods.
Weight variation - nmt than 2/12 mt 10% from mean; none more than 15%
physical stability.
UV assay - 98% - 101.5% in water at 207 min; written out procedure.
HPLC - new column dimensions, flow rate
TLC -

Comments:

Most of the problems stem from the choice of method. An ion pair method utilizing a reverse phase system would be preferable. As it now stands the sponsor's HPLC method is not suitable for regulatory purposes without confirmation via validation in our laboratories. The lack of reproducibility, drifting baselines and poor sensitivity make results difficult to interpret.

The data do not include pH or optical rotation which would be helpful confirmatory parameters.

. No data are presented to indicate any use for this method e.g. does it resolve anything else? The choice of weight variation as a stability parameter appears meaningless.

Data Summary:

(1)

45°C lot 84C019

3 wks UV assay 99.49; HPLC baseline drift; TLC "smearing of standard", but looks ok for sample.

10 wks UV assay 99.85; HPLC baseline drops off chart; TLC ok.
16 wks UV assay 99.14; HPLC appears same as standard; TLC illegible.

60°C lot 84C019

1 wk UV assay 99.98; HPLC ok; TLC standard is smeared -second spot.
3 wk UV assay 100.50; HPLC ok; TLC ok.

60°C lot 84C019

6 wks UV assay 99.72; HPLC ok; TLC judged ok some staining at solvent front.
10 wks UV assay 100.85; HPLC ok; TLC ok.
6 wks UV assay 99.59; HPLC ok; TLC ok.

40°C /80% R.H.

2 wks UV assay 98.08; HPLC peak tailing; TLC ok.
6 wks UV assay 99.82; HPLC look ok; TLC ok.
10 wks UV assay 100.57; HPLC erratic baseline; TLC ok.

"Ambient" temperature
13 wks UV 99.96 HPLC's equivalent; TLC ok.

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(2) Lot 014-007-82 used to make 82L051

m.p. 169-172; TLC ok; UV assay 99.22%; pH 2% soln. 4.85; submitted
HPLC p. 27 indicates gross "stepping" conditions were 1 ml/min = no resolution at all; TLC looks ok.

Initial 82L051: mp 75°C; TLC said adequate; HPLC 1 peak; UV 100.21% "stepping" of HPLC possible extra peaks run at 0.3 ml/min = no resolution TLC appears ok; IR similar to standard.

45°C

3 wks UV 100.27; HPLC looks ok; TLC looks ok.
10 wks UV 99.68; HPLC looks ok; TLC ok.
16 wks UV 98.92; HPLC ok; TLC ok.
24 wks UV 98.91; HPLC stepping; TLC ok.

60°C

1 wk UV 100.13; HPLC one peak ok; preceeds stnd; TLC smearing in sample.
3 wks UV 99.87; HPLC ok no baseline); TLC ok.
6 wks 100.28; HPLC stepping on sample; TLC ok.
10 wks 99.87; HPLC stepping; TLC ok.
16 wks 99.70; HPLC ok; TLC some smearing

40°C /80% R.H.

2 wks UV 100.74; stepping; TLC smeared on edge.
6 wks UV 100.28; HPLC similar; TLC ok.
10 wks UV 99.63; HPLC similar; TLC ok.
16 wks 100.05; HPLC large stepping; TLC ok.

Ambient
13 wks UV 100.14 HPLC/TLC ok.
26 wks UV 100.42; HPLC/TLC ok.
39 wks UV 99.92; HPLC/TLC ok.
12 mo. 99.49; HPLC ok; TLC not readable.
15 mo. 100.83; HPLC ok; TLC ok.
18 mo. 99.43; HPLC ok; TLC ok.

(3) 83 H067 was also made from bulk 015-00783

m.p. 76-77°C UV assay 100.71 standard HPLC shows stepping; TLC ok.

45°C

3 wks UV 99.67; HPLC erratic baseline; TLC ok.
10 wks UV 99.82; HPLC standard shows stepping; TLC ok.
16 wks UV 100.41; HPLC baseline erratic; TLC ok.
24 wks UV 99.26; HPLC ok; TLC ok.

60°C

1 wk UV 100.60; HPLC ok; TLC ok.
3 wks UV 100.31; HPLC shoulder on peak; TLC apparently ok.
6 wks UV 99.90; HPLC no baseline; TLC ok.
10 wks UV 99.74; HPLC stepping; TLC anomalous
16 wks UV 99.81; HPLC baseline?; TLC ok.

40°C /80% R.H.

2 wks UV 99.68; HPLC ok; TLC ok.
6 wks UV 99.72; HPLC ok but does not return to baseline; TLC ok.
10 wks UV 99.36; HPLC ok; TLC ok.
16 wks UV 100.01; HPLC no baseline; TLC ok.

Ambient
15 wks UV 100.18; HPLC erratic; TLC ok.
26 wks UV 99.67; HPLC ok; TLC ok.
39 wks UV 99.58; HPLC baseline drift; TLC ok.

Similar data exist for the bulk drug at ambient temperature.

Conclusions:
The data are erratic; the TLC and HPLC appear extremely dubious. The UV is non-specific.
The data are clearly inadequate as presented.

If the methods can be shown to be adequately discriminatory, and sensitive, a reasonable expiration date could be considered. pH and optical rotation data would be helpful. The stability of the aersol solution in contact with the components of the nebulizer should be assessed.

13. Labeling:

a) Container requires revision to enhance size of generic name and addition of "manufactured for."

b) Insert: Requires clarification as to whether other aerosol units may be employed. The stability references under "How Supplied" have not been supported by data and are confusing, e.g. if the drug is to be used for 7 hrs and is only stable for 6 hrs, what does "discard daily" refer to? The 0.75 retention value listed was previously $0.75^{5}$ with 5 as a superscript.

The labeling should also caution against admixture with other drugs. The desk copy of the 510(k) refer to use with assisted ventilation apparatus. The in-vitro delivery rate should be explored with common types of this appartus.

The M.O. should review the section re common problems with assisted ventilation since these are not reported in the New Drug Application.

14. Control Number: Adequate.

15. Inspections: Requested with this review.

16. Validation: Requested; Not possible with current methods.

17. GLP: Unknown.

18. Part 5 356H: Satisfactory

19. Environmental Impact: None anticipated at the Bureau level.

Draft of Chemist's Portion of Letter to the Sponsor

The application is non-approvable per 505(b)(4) and (b)(5) of the Act.

The following dificiencies are noted:

1. Failure to include complete characterization of the standard in order to establish its purity and suitability as a single standard for the new drug substance and the dosage form.

   a) The IR curves are undefined relative to . No interpretation has been provided. The Investigational New Drug Application contains numerous illegible, uninterpreted curves for the drug substance; possibly this information can be presented in a fashion to establish exactly what the reference IR spectra is. The dosage form is claimed to be and the IR differs. This should be rationalized.
   For regulatory purposes a clear standard is required.

   b) The TLC method employed determines one synthetic impurity per the submitted data. Does it separate other precursors or side reaction products? If so, what are the sensitivities?

   c)

   The development of a reproducible alternate method such as ion pair chromatography using a reverse phase column might be a worthwhile consideration along with the use of a sampling value and an internal standard or resolution marker. Im any event, systems suitability must be defined for all regulatory HPLC methods.

   d) The m.p. of the standard and of the new drug substances should be specified on the basis of corrected melting points.

   e) The submitted nmr for the drug fails to include relevant assignments or integrations. The latter may be part of the "computer code" which is not legible and included no explanations.

   f) Since the drug exists in at least curves would be helpful.

   g) The data should include specific rotation for the standard.

2. It fails to include adequate tests and specifications for the dosage form to assure identity, strength, quality and purity. In this regard:

   a) See comments above re IR, TLC, HPLC.

   b)

   c) pH and optical rotation specifications should be added.

   d) The weight variation specification should conform to USP XX.

   Since the drug is given in high dosages for prolonged periods, the regulatory methods proposed must be demonstrated to provide adequate specificity, sensitivity, reproducibility, accuracy and precision as written and employed.

3. The submitted stability data are difficult to interpret due to the analytical difficulties noted. Overall comment is reserved pending clarification. The following information is also requested:

   a) The results of developmental studies of forced degradation of the drug substance under the most likely conditions (acid hydrolysis, oxidation, photolysis).

   b) pH and optical rotation data for representative stability lots of the dosage form.

   c) The results of your compatibility studies of the aerosol solution with components of the nebulizer.

4. The container labeling requires revisions as follows:

   a) The generic name of the drug should be stated in type size at least one half that of the brand name.

   b) "Manufactured for" must precede your company name.

   c) It is suggested that the word "pure" preceding drug substance be deleted.

5. The package insert requires revision or clarification as follows:

   a) If the SPAG-2 aerosol generator is necessary for safe, efficacious delivery of the dosage form, the insert should so state. If not, those which are suitable should be listed and appropriate stability/compatibility data submitted.

   b) A warning should be added regarding admixture of other drugs with the ribavirin solution.

   c) The stability parameters cited require clarification. If the drug is only stable for six hours at room temperature, a seven hour delivery would seem unwise.

Refrigerated stability data and room temperature compatibility data are requested.

d) It is noted that previous draft labeling lists a retention factor of 0.7, while current labeling list 0.75.

e) Delivery rate (in-vitro) studies are required for standard assisted ventilation techniques.

f) Under "Description", the word sterile should precede USP water for injection.

6. Additional information has been requested from concerning their Drug Master File submission on your behalf.

7. For clarity, it would be helpful to withdraw the previous contract facilities from the application, and to state who will perform final testing on the finished product.

Please also submit a copy of the lyophilization procedure employed by your current contractor.

Drug Products
Chemist's Review (3)
Date Completed: 12/19/84

A.1. NDA 18-859

Sponsor: Viratek, Inc.
Covina, CA 91722

2. Product Names:

Generic: ribavirin

Proprietary: Virazole

3. Dosage Form & Route of Administration: cryodessicated sterile solid for aerosol administration after dilution with sterile water for injection.

4. Pharmacological Category and/or Principal Indication:

5. Structural Formula and Chemical Name(s):

1-β-D-ribofuranosyl-1,2,4 triazole-3-carboxamide

B. 1. Original Submission: 9/12/82; (review #1 1/19/83, Kochert)

2. Control Amendments: 9/11/84; 9/14/84; 9/17/84; 9/25/84 review #2 (Taylor 10/16/84); 10/27/84 subject of this review.

3. DMF Referrals:

C. Remarks:
The submitted HPLC curves are of such poor quality as to be uninterpretable by this reviewer. This validation data developed by Baylor University demonstrates erratic peak heights, and unexplained impurities. The comments written on the Baylor HPLC curves are primarily illegible. Some of the stability data were evidently generated at
- there are no data verifying adequacy of the system under these conditions.

The sponsor wishes specifications of a total of 1.5% of any or all impurities. Due to the dosage of this drug this would appear excessive unless the pharmacologic action of the impurities is known or has been investigated.

18-859 Review #3 Notes

1&2. Components and Composition: N/C

3&4. Facilities and Personnel

5. Synthesis

Eastman p
materials
precursor

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...ward.

The use of a 98.5% peak height vs. stnd. would have no utility as a purity value for this system. Either peak height total % or A% of all impurities should be utilized for release purposes - assuming it can be demonstrated that a method of the sponsor's choice works. Additionally a limit should be provided for each individual impurity.

The rationale for requiring rigorous methods for this dosage form is that it is given in a dose of 6 grams. Assuming a 1% impurity level and neglecting unknown retention factors a 60 mg dose of impurity could be given to the patient per day. Unless the pharmacologic/toxicologic nature of these impurities is known or has been investigated, this would appear unwise.

7. Other Firms: N/C

8. Manufacturing and Processing: N/C

9. Container: N/C

10. Packaging & Labeling: N/C

11. Controls (Finshed Dosage Form): The sponsor states that an lyophilized standard will be employed for IR reference. No data or spectra are provided.

Recommendation: If the lyophilized dosage form can be appropiately recrystallized to either the $V_1$ or $V_2$ polymorph, this would be more useable than a system of mixed polymorphic IR standards.

12. Stability:
Comment reserved pending clarification of method adequacy. pH, optical rotation data appear adequate. The curves indicate that the lyophilized dosage form is indeed

13. Control Numbers: N/C

14. Methods Validation:
A preliminary review of the methods was requested 12/11/84, by HFN-420 to at least delineate what problems are apparent. The recent submission will also be provided to our laboratories for their comments on the anomalous TLC results.

15. Labeling:
The container label requires "brand of" between "Viratek" and "Ribavirin". The potency should be stated on the main panel. Storage conditions should be added.

16. Inspections: Previously requested.

17. A concurrent review by Medical Devices is required.

Chemist' Portion Draft Letter to the Sponsor

The application is non-approvable per 505(b)(4) and 505(b)(5) of Act as follows:

1. The intention to utilize a lyophilized standard as the infrared identity standard for the dosage form is noted. This standard must be defined by comparison to the lots utilized. Alternatively perhaps a recrystallization procedure for the dosage form may provide a consistent IR for comparison to either the
In either case please provide all relevant spectra run under the same conditions and with the same instrumentation parameters. Due to possible "noise" and instrumental/variation we have been unable to consistently interpret previous spectral results.

2. We are presently unable to concur with your assessment of the adequacy of the HPLC procedure. The shifting baselines in your own data, the lack of reproducibility (peak heights) in the Baylor data, the low sensitivity demonstrated, at ender consistent interpretation of the data extremely difficult. Many of the previously submitted HPLC curves for your product have failed to demonstrate baseline recovery. Coupled with the Baylor data, we are incapable of determining consistently the stability of the drug or the presence of impurities. Perhaps this may be due to "productions runs" done rather hurriedly. We have referred this matter to our Division of Drug Chemistry for comment. Pending such comment, we are unable to draw scientifically valid conclusions.

   In the interim we request the following:

   a) Clarification of the actual HPLC method which will be employed for impurity quantitation. Evidently, will employ a different method from Viratek.

   b) For whatever method is to be employed adequate data are required which should include systems suitability, linearity/sensitivity for each impurity and carefully defined quantitation. In regard to impurity quantitation both a total impurity % limit and individual impurity % limit are required. Any impurity approaching the 0.5% level should be identified and quantitated. We do not regard peak height comparisons to the standard as useable in this system. As previously stated the elution of the drug on the solvent front under all conditions in the application/DMF requires demonstration that other impurities/degradation products do not elute in the same area. Your data re oxidation of the drug for example, shows no change in peak height. The peak areas are different apparently. With a sugar moiety we would anticipate formation of a under the conditions used. Evidently the may elute with the drug. Similarly the stability studies in water evidence peaks which do not return to baseline. Please provide useable data. Perhaps the column was not allowed to equilibrate between runs due to the pressure of time, but we cannot use the date submitted.

c) The data submitted by Baylor University indicate non-reproducibility of peak heights for the drug. You may wish to confirm this by appropriate analysis. The sensitivity limits at 1, 2, 4, and 6% total appear marginal and from your data we cannot determine levels because of baseline shifts.

In addition, the Baylor data indicate additional non-identified impurities which require clarification.

d) Please provide a quantitated impurity profile analysis for several lots utilized in clinical studies.

3. Final comment on stability studies is reserved pending resolution of the analytical difficulties previously noted. It should be recognized that ultimately additional studies utilizing a validated method may be necessary. At this time however, we request clarification of data generated at 0.6 ml/min, 4mm column diameter -- is this a typographical error?

Additionally revision of the general protocol is suggested to include at least monthly testing for accelerated samples and quarterly testing of samples added to the protocol due to process changes. Additionally, sterile samples should be tested for sterility on an annual basis. Proposed guidelines are available per the Federal Register announcement of April 18, 1984.

4. The container labeling requires revision to include "brand of" between "Viratek" and "Ribavirin". Storage conditions should be added. The potency should preferably be stated on the main panel.

5. Additional information has been requested from . Their data for TLC indicates the method will detect impurities. One consistent impurity appears which may require semi quantitation and possibly full identification. Again without relevant sensitivity data, as was previously requested, the data are not amenable to analysis.

As previously noted, the HPLC method proposed for use by differs from that proposed in the New Drug Application. We suggest that a consistent method be utilized after appropriate studies.

Division of Anti-Infective
Drug Products
Chemist's Review #4
Date Completed: 6/6/85

A.1. NDA 18-859

Sponsor: Viratek, Inc.
Covina, CA

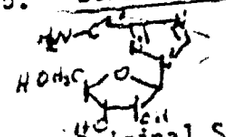
2. Product Names:

Proprietary: Virazole
Generic:(USAN): ribavirin

3. Dosage Form & Route of Administration: Sterile 6 gm lyophilized solid for aerosol administration after dilution with sterile water for injection or inhalation to 20 mg/ml.

4. Pharmacological Category and/or Principal Indication: RSV treatment

5. Structural Formula and Chemical Name(s):



1-B-D-ribofuranosyl - 1,2,4 triazole -3- carboxamide

B. 1. Original Submission: 9/12/82 (review #1: 1/19/83)

2. Amendments: See review #1, 2, 3

This Review:

1/8/85 - HPLC precision and sensitivity data

1/17/85 - TLC data for
HPLC data for

2/18/85 - general chemistry update

3/28/85 - revised stability protocol

4/15/85 - new Contractors

4/16/85 - contamination data (none found 0.5%)

4/22/85 - revised SPAG - 2 manual

5/3/85 - SPAG - 2 information

5/9/85 - m.p. information on lyophilized material

5/9/85 - new stability protocol

5/21/85 - lyophilization procedure.

3. Drug Referrals: 2nd supplement HPLC and TLC data (not dated)
4/25/85 - reaction rate data

C. Remarks:
The sponsor has made a concerted effort to address the controls deficiencies. The remaining questions noted in the attached deficiency list can be corrected with reasonable effort.

D. Conclusions and/or Recommendations:
The application remains non-approvable. The attached list of deficiences, however, does not appear to require substantial additional research assuming the sponsor has maintained adequate investigational records.

A list of proposed impurity limits for the dosage form is attached for the pharmacologist's assessment with pertinent comments from this reviewer as to sensitivities and clinical lot histories.

Methods validation is mostly complete. The report from HFN - 420 is attached. Questions remain regarding the m.p. and purity of the dosage form. Inspections have been re-requested with this review.

John W Taylor
John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Taylor: gm 6/11/85
HFN-815/Browder
R/D Init. by: ARCasola 6/7/85 ARC 6/14/85
HFN-815/MO
4238b

Reviews Notes:

1&2. Components and Composition: N/C.

3. Facilities:
a) The new drug substance will now be produced solely by

b) The drug dosage form will now be manufactured by either:

c) Analytical controls will be evidently performed on the dosage form by Viratek, Inc. Sterility testing will be performed by facilities in b). See item 8. The procedure require clarification.

4. Personnel: N/C.

5. Synthesis: N/C. See previous review for

6. Raw Material Control: See methods validation.

7. Other Firms: Per item 3.

8. Manufacturing and Processing:
The description of the lyophilization process performed by includes two cautions - one for yellow light use only and one concerning a residue left on the equipment by the drug solution. Since Viratek, Inc. claims the drug is not and larification is required. It is unclear who will perform final product testing from the mfg sheet. If a residue exist; it should be verified to be authentic ribavirin.

9. Container/Closure:

Comment: DMF's are required. Stability protocol must include each type.
b) container: Glass vial. Should specify type per USP.

Comment: A 100 ml vial will require two or three transfers to form a 20 mg/ml solution. Firm should supply relevant instructions re preparation and list volume in insert.

10. Packaging and Labeling: Adequate.

11. Controls: See methods validation section.

12. Stability:
On balance the sloppy data previously submitted by the firm do not indicate an unstable product. Based on the revised protocol submitted, a 24 month expiry period is tentatively acceptable provided the sponsor submits as part of the reports representative HPLC recordings so that a clear understanding that drifting baselines etc. will not be accepted for any extensions of dating. The data submitted also indicate:

a) the drug is not photosensitive
b) is resistant to oxidation
c) is stable for about 24 hours at least in aqueous soln.

The employed requires refinement as noted in previous reivews.

13. Control Numbers: Satisfactory.

14. Methods Validatations:
HFN-420 has completed an initial evaluation and the results are attached for inclusion in the NDA file. The nature or cause of the m.p. variation in the lyophilized dosage form remains a concern to this reviewer. The sponsor's explanations while facile are not easily reconciled with basic laws of physical chemistry (freezing point depression). Due to the nature of impurity controls , the possibility remains that an unknown impurity exists. HFN-420 has been instructed to solicit samples displaying this phenomenum and to evaluate same.

Overall this reviewer with the exception of the points attached under "Impurity Profiles" agrees with HFN-420 in their evaluations and these issues will be addressed to the sponsor both for the n.d.s. and the dosage form which are apparently identical except in m.p. as noted in previous rviews. The instructions from (item 8) lend further confusion to this situation.

A research commitment will also be requested from the sponsor to improve the method. This commitment should embody testing typical and providing this reviewer with quarterly results as part of the required periodic reports.

15. Labeling:
a) Container; N/C. Requires revision as previously requested.

b) Insert: N/C. Requires revision as previously noted.

c) SPAG -2 Instructions: The key warning should be in talics or underlined.

Separate, complete instructions should be issued for the assisted ventilation procedures with stating that 8a, c etc, do not apply.

16. Inspections: Re-requested.
Conversation with Ms. O'Rourke on 5/23 indicated these were "lost" during reorganization of compliance. 4 requests issued and are part of the NDA file. The updated request (re-issue) is attached for our records. The original was signed 5/28 by the supervisory chemist who was advised of the problems with HFN-322.

17. N/C/

18. N/C.

19. Additional Material:
This reviewer is of the opinion that additional drug delivery data should be required for the assisted ventilation procedure both with and without use of the drying chamber under pressures, etc. which concur with the instruction manual. The firm has stated that the mean mass diameter does not change much in distribution but no data have been provided.

This was previously requested in review #2. Ultimately, a decision must be made either by a M.O. or a respiratory therapist as to whether this question has been satisfactory addressed by the sponsor.

20. Additional comments are reserved pending consultation with our Bureau of Medical Devices.

NDA 18-859

OUT

## Impurity Profiles (Known)

I. Structures

NDA 18-859

Draft Chemist's Portion of Letter to Sponsor

The application remains non-approvable per 505(b)(4)(5) and (6) of the Act. The following deficiencies and/or comments are provided.

1. Due to observed differencies in response factors it has become evident that the HPLC method for the impurity analysis in the active ingredient and dosage form requires modification.

The necessary factors are as follows:

a) Actual impurity standards must be incorporated in the method to allow wt/wt quantitation.

b) The purity of these (impurity) standards and their preparation must be delineated in a manner allowing utilization and reproduction in our laboratories. UV spectra of the impurities would be helpful.

c) The methods for both the n.d.s. and the dosage form must be rewritten to provide a step-by-step procedure allowing weight percentage determinations for the impurities. The methods should be written as proposed for routine use.

d) Systems suitability parameters must be defined i.e. a maximum rel. stnd. deviation for replicate injections, a maximum peak assymetric or tailing factor, and minimum resolution factors should be delineated. A re-equilibration time for the column should be incorporated based on the most retained compound.

2. Analysis of the submitted lot histories indicate that less than of any impurity has been observed. The specifications should be revised downward accordingly.

3. The submitted procedure from evidently requires the use of during production and mentions the difficulty in . Since available data indicate the drug is not and is please clarify these requirements for your contractor. If a residue exists, an analysis should be conducted to identity and confirm that it is indeed ribarivin.

Please also state for this contractor exactly who will perform release analysis and sterility testing.

4. The submitted container labeling requires revision as noted previously. "Manufactured for" or "distributed by" must procede your company name. "Ribavirin" must be in type size at least 1/2 that of "Virazole." "Brand of" must be inserted between "Viratek" and "Ribavirin." The storage conditions should be on the container label.

NDA 18-859

## Impurity Profile Analysis

I. Available Lot Histories/Analytical Results

A. Viratek's Lot Histories

B.

C.

D.

5. Since the product is packaged in a 100 ml vial thought should be given to providing convenient directions for aseptic dilution to 300 ml. It is also suggested that the "How Supplied" section of the insert specify the volume of the vial.

6. Our Division of Drug Chemistry has completed a preliminary evaluation of the proposed methods. They have the following additional comments:

a)

b) The mobile phase should be utilized for sample dissolution in the HPLC methods to avoid disturbancies at $t_o$.

c) An upper limit should be provided for the assays for the new drug substance and dosage form.

d)

7. A research commitment is requested to attempt to define a more adequate HPLC procedure. Specifically the use of and the should be explored and results reported as part of the required periodic reports.

8. The submitted stability data may permit the use of a tentative two year expiration date under the conditions of your proposed revised protocol. Since the previous data were erratic due to developing analytical methods, your commitment to submit representative chromatograms and TLC plates is requested as part of the data.

9. Drug Master File referrals are required for each proposed stopper. The description of the container should be corrected to specify Type I glass.

E. Conclusions:

The HPLC method can be used for the three impurities above in the range of about

Due to differencies in columns and detectors defined impurity standards are required to be run, and systems suitability should be appropriately defined.

It would appear that the proposed for each impurity limit is too high from the lot histories. The firm will be asked to propose lower limits and a total limit of From the data and giving margin for error no impurity should exceed and the total should not exceed The actual impurity standards also require a) definition of purity and b) synthetic routes since they are not commercially available. UV absorbance spectra would be useful for defining relevant responses factors.

Our laboratories have requested a method for . The reaction rate data from indicate that this material is very unlikely to be formed and that the is that most resistant to . Therefore, this will not be pursued.

HPLC data submitted by both and Viratek indicate is not a contaminant.

Division of Anti-Infective
Drug Products
Chemist's Review (#5)
Date Completed: 6/21/85

A.1. NDA 18-859

Sponsor: Viratek, Inc.
Costa Mesa, CA 92626

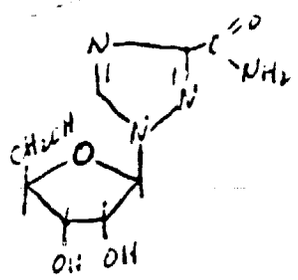
2. Product Names:

Proprietary: Virazole
Generic:(USAN): ribavirin

3. Dosage Form & Route of Administration: Sterile 6 gm lyophilized solid for aerosol administration after dilution to 20 mg/ml with sterile water for injection or inhalation.

4. Pharmacological Category and/or Principal Indication: RSV treatment

5. Structural Formula and Chemical Name(s):



1-B-D-ribofuranosyl - 1,2,4 triazole -3- carboxamide

B. 1. Original Submission: 9/12/82 (review #1, W. Kochert 1/19/83) reviews (#2, #3, #4, #5, Taylor)

2. Amendments: See reviews 2-4

Current: 6/7/85 - Clarification of m.p.; TGA curves
6/20/85 - Corrected chemistry, labeling
W/D as contractor
(2) 6/18/85 - Insert labeling , W/D

3. DMF Referral: See review (#4)

C. Remarks:
In conjunction with , the sponsor has corrected the chemistry as agreed to in our meeting of 6/19/85. (See NDA file for minutes.)

D. Conclusions and/or Recommendations:
The application is approvable as per mfg. and controls section submitted with draft labeling.

EIR's are pending.

John W. Taylor

John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Taylor: gm 6/24/85
HFN-815/Browder
R/D init. by: ARCasola 6/24/85

Division of Anti-Infective
Drug Products
Chemist's Review (#5)
Date Completed: 6/21/85

A.1. NDA 18-859

Sponsor: Viratek, Inc.
Costa Mesa, CA 92626

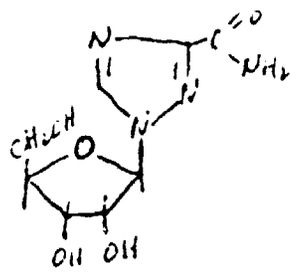
2. Product Names:

Proprietary: Virazole
Generic:(USAN): ribavirin

3. Dosage Form & Route of Administration: Sterile 6 gm lyophilized solid for aerosol administration after dilution to 20 mg/ml with sterile water for injection or inhalation.

4. Pharmacological Category and/or Principal Indication: RSV treatment

5. Structural Formula and Chemical Name(s):



1-B-D-ribofuranosyl - 1,2,4 triazole -3- carboxamide

B. 1. Original Submission: 9/12/82 (review #1, W. Kochert 1/19/83) reviews (#2, #3, #4, #5, Taylor)

2. Amendments: See reviews 2-4

Current: 6/7/85 - Clarification of m.p.; TGA curves
6/20/85 - Corrected chemistry, labeling
W/D as contractor
(2) 6/18/85 - Insert labeling , W/D

3. DMF Referral: See review (#4)

C. Remarks:
In conjunction with , the sponsor has corrected the chemistry as agreed to in our meeting of 6/19/85. (See NDA file for minutes.)

D. Conclusions and/or Recommendations:
The application is approvable as per mfg. and controls section submitted with draft labeling.

(EIR's are pending.)

John W. Taylor

John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Taylor: gm 6/24/85
HFN-815/Browder

Division of Anti-Infective
Drug Products
Chemist's Review #5
Date Completed: 6/21/85

A.1. NDA 18-859

Sponsor: Viratek, Inc.
Costa Mesa, CA 92626

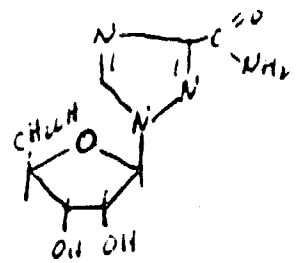
2. Product Names:

Proprietary: Virazole
Generic:(USAN): ribavirin

3. Dosage Form & Route of Administration: Sterile 6 gm lyophilized solid for aerosol administration after dilution to 20 mg/ml with sterile water for injection or inhalation.

4. Pharmacological Category and/or Principal Indication: RSV treatment

5. Structural Formula and Chemical Name(s):



1-B-D-ribofuranosyl - 1,2,4 triazole -3- carboxamide

B. 1. Original Submission: 9/12/82 (review #1, W. Kochert 1/19/83) reviews #2, #3, #4, #5, Taylor).

2. Amendments: See reviews 2-4

Current: 6/7/85 - Clarification of m.p.; TGA curves
6/20/85 - Corrected chemistry, labeling
W/D Ben Venue as contractor
(2) 6/18/85 - Insert labeling , W/D Ben Venue

3. DMF Referral: See review #4

C. Remarks:
In conjunction with Eastman Kodak, the sponsor has corrected the chemistry as agreed to in our meeting of 6/19/85. See NDA file for minutes.

D. Conclusions and/or Recommendations:
The application is approvable as per mfg. and controls section submitted with draft labeling.

EIR's are pending.

John W. Taylor

John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Taylor: gm 6/24/85
HFN-815/Browder
R/D Init. by: ARCasola 6/24/85
HFN-815/MO
4368b

ARC 6/26/85

PHARM

REV

8,5-FILE

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 18-859 (Amendment, dated 3/15/85)

Date Review Completed: 5/3/85

Applicant: Viratek, Covina, CA

Drug: Ribavirin (Virazole) Aerosol

Category: Antiviral

Comments: Background Information on previously performed preclinical studies can be found by reference to pharmacology reviews contained in NDA's 18-859

The final reports of the 10- & 30-day repeat exposure inhalation toxicity studies in suckling ferrets were submitted by Viratek in an amendment to their NDA #18-859, dated 3/15/85. A review & evaluation of these studies follows.

TOXICITY STUDIES

Aerosol Inhalation Toxicity Study: Ferret

Lab Perf. Study:

Proj. Report No.:

Material Tested: Ribavirin dissolved in water

Purity or Stability: Data on the test compound was not submitted by the applicant to the investigator.

Lot Nos. Used: Viratek Lots 84C019 & 84D048; , 10121-003 & -004

Reservoir Conc'n: 32 vials drug + 1920 ml water = 800 ug/L; 16 vials drug + 960 ml water = 400 ug/L; 8 vials drug + 480 ml water = 200 ug/L

Mean Drug Conc'n Achieved in Exposure Chambers: Vehicle control (water); 162 ± 30 ug/L (LD); 355 ± 63 ug/L (MD); 620 ± 96 ug/L (HD)

Approx. Exposure Doses of Kits: In terms of mg/kg/day, LD = 59.94; MD = 131.35; HD = 229.4

Mean Particle Size Distribution in Exp. Chamber (uM): LD = 1.54; MD = 1.72; HD = 1.88

Route & Duration: Inhalation exposure via whole-body dynamic exposure chamber for 6 hrs/day for 10 & 30 days

Measurements Made in Exposure Chamber: Rate of air flow, actual conc'n of drug in breathing zone (meas. made 6x/day), temp. & humidity (hourly), particle size distrib. (prestudy & once/wk for 4 wks)

Species & Sex Tested: Suckling ferrets littered by non-primaparous dills

Table 1
Distribution of Ferret Jills & Kits Between Dose Levels

| Group No. | Exposure Levels Level | Conc. ug/l | Gp A (10-day Exposure) Jills | Male Kits | Female Kits | GP B (30-day Exposure) Jills | Male Kits | Female Kits |
|---|---|---|---|---|---|---|---|---|
| 1 | Vehicle | 0 | 2 | 6 | 9 | 4 | 12 | 12 |
| 2 | LD | 162 | 2 | 6 | 9 | 4 | 12 | 12 |
| 3 | MD | 355 | 2 | 6 | 9 | 4 | 12 | 12 |
| 4 | HD | 620 | 2 | 6 | 9 | 4 | 12 | 12 |
| Totals | | | 8 | 24 | 36 | 16 | 48 | 48 |

Exposure Time: 6 hrs/day for 10 & 30 consec. days

Disposition of Kits & Surviving Jills: At termination of 30 days exp., kits were either weaned or handled as shown in the following table; most of the surviving jills were killed and subjected to gross & histopath. exam (pituitary, mammary & adrenal glands, ovaries, lungs, liver & kidney).

Table 2
Scheduled Disposition of Ferret Kits
in Group A (10-Day Exposure) & Group B (30-Day Exposure)

| | Control | | | | Low | | | | Mid | | | | High | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GR.1A | | GR.1B | | GR.2A | | GR.2B | | GR.3A | | GR.3B | | GR.4A | | GR.4B | |
| Exposure Duration | 10d | | 30d | | 10d | | 30d | | 10d | | 30d | | 10d | | 30d | |
| Sex | M | F | M | F | M | F | M | F | M | F | M | F | M | F | M | F |
| 1. Expose | | | | | | | | | | | | | | | | |
| -for 10 days | 6 | 9 | - | - | 6 | 9 | - | - | 6 | 9 | - | - | 6 | 9 | - | - |
| -for 30 days | - | - | 12 | 12 | - | - | 12 | 12 | - | - | 12 | 12 | - | - | 12 | 12 |
| 2. Sacrifice After | | | | | | | | | | | | | | | | |
| -10 Day Exp. | - | 6 | - | - | - | 6 | - | - | - | 6 | - | - | - | 6 | - | - |
| -30 Day Exp. | - | - | 6 | 6 | - | - | 6 | 6 | - | - | 6 | 6 | - | - | 6 | 6 |
| -20 Day Recov. | - | 3 | - | - | - | 3 | - | - | - | 3 | - | - | - | 3 | - | - |
| -120 Day Recov. | - | - | 6* | 6* | - | - | 6* | 6* | - | - | 6* | 6* | - | - | 6* | 6* |
| -140 Day Recov. For Special Studies of Lungs | 6* | - | - | - | 6* | - | - | - | 6* | - | - | - | 6* | - | - | - |
| 3. Pulmonary Function Eval. | | | | | | | | | | | | | | | | |
| -After Expos. | - | - | 6 | 6 | - | - | 6 | 6 | - | - | 6 | 6 | - | - | 6 | 6 |
| -20 Days Later | 6 | - | - | - | 6 | - | - | - | 6 | - | - | - | 6 | - | - | - |
| -120 Days Later | - | - | 6* | 6* | - | - | 6* | 6* | - | - | 6 | 6* | - | - | 6* | 6* |
| -140 Days Later | 6* | - | - | - | 6* | - | - | - | 6* | - | - | - | 6* | - | - | - |

*These do not represent different animals. Pulmonary function measurements were taken twice on the same animals. Special tests were conducted on 3/sex/dose level after the pulmonary function assessments were completed.

Age of Kits at Initiation of Exposure: 10 days

Parameters Evaluated: Kits: Abnormal behavior, signs of toxicity or pharmacologic effects (10, 12, 15 & 20 days of age and weekly thereafter throughout the test period); body wts at the same time & at the end of exp.; mortality/morbundity checks (jills & kits daily throughout the test).

Special Studies

1. Pulmonary Function

| Time of Test | Age of Animals | No. of Animals |
|---|---|---|
| Immediately after 10-day exposure | 20 days | None* |
| 20 days " " " | 40 " | 6 M/dose gp |
| **140 days " " " | 150 " | 6 M/dose gp |
| Immediately " 30-day " | 40 " | 6/sex/dose gp |
| 120 days " " " | 160 " | 6/sex/dose gp |

*Why were these not performed?
**Measurement will be made if changes are seen at 40 days of age.

Parameters Measured

a) Tidal volume & respiration rate & their product (minute volume)
b) Pulmonary resistance & compliance
c) Flow volume analysis
d) Quasistatic compliance of the lung

2. Lung Lavage Studies

| Time of Test | Age of Animals | No. of Animals |
|---|---|---|
| Termination of 10-day exposure | 20 days | 3 F/dose gp |
| After 10-day exp. + 140-day recovery | 160 " | 3 M/dose gp |
| " 30-day exposure | 40 " | 3/sex/dose gp |
| " " " + 120-day recovery | 160 " | 3/sex/dose gp |

Parameters Measured: No. of lavagable cells/unit volume of lavage fluid and ratio of AM (alveolar macrophage) to PMN (polymorphonuclear) cells calculated. According to the investigator, "a decrease in this ratio (i.e., a relative inc. in PMN's) in the lavage fluid would be an indication of inflammation of the lung."

3. Lung Histopathology & Morphometry: (Alveolar size determination)

| Time of Test | Age of Animals | No. of Animals |
|---|---|---|
| After 10-day exposure | 20 days | 3 F/dose gp |
| " " " + 20-day recov. | 40 " | 3 F/dose gp |
| " " " + 140-day " | 160 " | 3 M/dose gp |
| " 30-day " | 40 " | 3/sex/dose gp |
| " " " + 120-day " | 160 " | 3/sex/dose gp |

4. Lung DNA Content: According to the investigator's report, "The lungs of all kits that recieved pulmonary lavage were not discarded as originally scheduled, but were saved after the lavage procedure was complete" and analyzed for DNA content.

| Time of Test | Age of Animals | No. of Animals |
|---|---|---|
| After 10-day exposure | 20 days | Analysis not submitted |
| " " " + 140-day recov. | 160 " | 3 F/dose gp |
| " 30-day " | 40 " | 3/sex/dose gp |
| " " " + 120-day " | 160 " | 3/sex/dose gp |

5. Blood Sample Collection: Collected at each scheduled sacrifice (i.e., after 10 & 30 days exp.) from 3 animals/sex/dose. Blood from each sex/gp was pooled & analyzed for drug and/or its metabolites.

6. Terminal & Postmortem Exam:

- Complete necropsies of all animals found dead or killed at termination (including jills killed upon weaning of kits)
- Organ wts & lungs examined in all scheduled kill kits and all animals killed at termination (not including jills)
- Tissues saved from all scheduled kill kits (lungs with mainstream bronchi, trachea, all tissues with gross lesions). "Entire carcass preserved in formalin (except culled kits & all animals used for lavage)."

7. Histopathology Evaluation

Tissues Examined: Lungs, bronchi & trachea of same animals killed for morphometry. "Histopath. done on same lobe of lung as used for morphometric measurement."

Intercurrent Death Kits: Histopath. of lungs, liver, kidney, spleen, heart, adrenal gland & stomach

Jills: Histopath. of pituitary, mammary & adrenal glands, ovary lung, liver & kidney. Remaining tissues & carcasses were preserved.

Results

Mortality

Kits Found Dead or Sacrificed Moribund

| 10-day exposure | | | | 30-day exposure | | | |
|---|---|---|---|---|---|---|---|
| Control | 162ug/L | 355ug/L | 620ug/L | Control | 162ug/L | 355ug/L | 620ug/L |
| 1/15 | 1/15 | 8/15 | 6/15 | 1/24 | 6/24 | 14/24 | 23/24 |

According to the investigator, "at necropsy, most of the kits were thin and their gastrointestinal tracts were empty. The probable cause of death was starvation due to lactation failure of the jills exposed to the two higher dose levels of test article aerosol."

Body Wt

10-day Exposure

162ug/L: No drug-related effects

355 & 620ug/L: Inhibition of body wt gain throughout exp. (stat. sig. at 3-5 days). Recovery occurred after exp.; however, wts persistently remained lower than controls to terminal necropsy.

30-Day Exposure

162ug/L: Inc'd wt over controls

355ug/L: Stat. sig. dec'd body wt gain from day 5 of exp. onward. Recovery occurred after exp.; however, wts remained lower than controls to terminal necropsy (stat. sig. lower than controls for 3 mos. after exp.)

620ug/L: Stat. sig. dec'd body wt gain at all weighing intervals during exp. Recovery occurred after exp.; however, wts remained lower than controls to terminal necropsy.

Comment: According to the investigating laboratory, body wt change trends were "in all probability a reflection of the lactation problems experienced first by the high dose jills and subsequently by the mid dose jills."

Pharmacotoxic Signs: (Initiation of Study through Week 6)

| Generalized or Local Hair Loss: | 10-Day Exposure | 30-Day Exposure |
|---|---|---|
| | 1/15 @ 620ug/L | 10/24 @ 355ug/L<br>8/24 @ 620ug/L |

| Animals Thin: | 10-Day Exposure | 30-Day Exposure |
|---|---|---|
| | 7/15 @ 162ug/L<br>15/15 @ 620ug/L | 21/24 @ 355ug/L<br>22/24 @ 620ug/L |

Gross Necropsy

a) Mean Individual Lung Weights
b) Mean Indiv. Lung/Body Wt Percents

| | After 10-Day Exp. + 20-Day Rec. | After 30-day Exp. | Aft 10-Day Exp. + 40-Day Rec. | Aft 30-Day Exp. + 120-Day Rec.* |
|---|---|---|---|---|
| a) | D @ 162 & 620ug/L. | D @ 162ug/L. | D @ 162, 355 & 620ug/L | D @ 162ug/L<br>I @ 355ug/L |
| b) | D @ 162ug/L<br>I @ 620ug/L. | D in F @ 162ug/L<br>I in M @ 162ug/L | I @ 162ug/L<br>D @ 355 & 620ugL | D @ 162ug/L<br>I at 355ugL |

*620ug/L animals died before scheduled necropsy.
D = decrease; I = increase

c) Gross & Microscopic Pathology Findings: See Tabulation, Appendix A

d) Pulmonary Function: See Appendix B

Lung Lavage Studies: At day 20 after 10-day exp., there was a dec'd no. of lavaged cells at the MD & HD levels. Cell viability for the LD & MD levels were comparable to controls; 1/2 animals at the HD level showed dec'd cell viability. For the control & drug-treated groups (all dose levels), 97-100% of cells recovered were alveolar macrophages. Peroxidase positive macrophages were inc'd in the HD group.

At week 6 after 30-day exp., HD animals died before determinations could be made. Dose-related dec'd no. of lavaged cells were seen at the LD & MD levels. Mean cell viability for the LD F was comparable to controls, while at the MD level, mean cell viability was dec'd due to low cell viabilities in 1/2 animals. In M, mean cell viability at the LD & MD levels were inc'd over controls due to low cell viability in 1/3 control M. For the control & drug-treated groups (all dose levels), 98-100% of the cells recovered were alveolar macrophages. Mean peroxidase positive macrophage values were inc'd in the LD & MD F. This inc. was attributed to high values seen in 1/3 animals in the LD group (e.g., inc. explained as being due to "the presence of bacteria which were phagocytized by macrophages and caused the influx of new macrophages into the lung") and in 1/2 animals in the MD gp (no reason given for the inc. seen in this animal). See Appendix C for tabulated data.

The applicant attempted to relate the dec'd no. of lavaged cells at the MD & HD levels after 10 & 30 days exp. to the dec'd body & lung wts resulting from drug effect on lactation of the MD & HD exp. mothers. The applicant tried to "normalize the lavaged cell numbers and express them as per gram of lung." However, the only groups for which this relationship can be accurately made are the control & LD M & F 30-day exp. groups, as these were the only groups for which actual lung wts were obtained. Actual lung wts were not obtained for control, LD, MD or HD 10-day exp. and MD & HD 30-day exp. groups. A comparison of the actual & estimated lung wts submitted by the applicant and conversion of these values to no. of cells lavaged/gram of lung shows a dec'd no. of the latter at the LD level, when correct actual values are used as compared to the applicant's estimated values (see table below).

| Group | No. | Actual Lung Wts (Raw Data) | Lung Wts Est. by Sponsor (Tabular Data) | # of Cells Lavaged/gm of Lung ($\times 10^{-7}$) Based on Actual Lung Wts | Based on Est. Lung Wts |
|---|---|---|---|---|---|
| Control | 6 | 3.94 | 3.96 | 1.489 | 1.469 |
| Low Dose | 6 | 3.83 | 3.31 | 1.303 | 1.524 |

At 10 days exp. followed by 140 days rec., animals of the MD & HD exp. groups died due to lactation failure of the mothers. Consequently, lavage was performed on lungs of the control & LD animals only. Ten-day exp. animals followed by 140-day rec. showed no change in mean no. of lavaged cells, dec'd mean cell viability, and inc'd mean peroxidase positive macrophages at the LD level (inc. due to high values seen in 1/2 LD animals; reason for inc. unexplained by the applicant). 85-86% of recovered cells were alveolar macrophages, which was comparable to macrophage rec. in the control group.

At 30 days exp. followed by 120 days rec., animals of the MD & HD groups died due to lactation failure of the mothers. Lavage performed on LD animals showed an effect in M consisting of dec'd mean no. of lavaged cells & cell viability and inc'd % lymphocytes; only 84% of recovered cells were alveolar macrophages compared to control rec. of 95%. (See Appendix D for tabulated data.)

Alveolar Size Determinations

Lab Perf. Study:

Project Rpt. No.:

Results: See Appendix D

After 10 & 30 Day-Exposure: A dose-related inc. (not stat. sig.) in mean alveolar diameter was seen immediately after 10-day exp. at the HD and at the LD & HD after 20-day rec. (stat. sig.). Inc'd mean alveolar diameter was seen immediately after 30-day exp. at the LD (stat. sig.). Alveolar size determination for the MD level after 10-day exp. + 20-day rec. and for the MD & HD levels after 30-day exp. were not obtained due to death of these groups before scheduled sacrifice. (See Appendix E for tabulated data.)

After 140 & 120-Day Recovery: After 10-day exp. + 140-day rec. there was dose-related dec'd mean alveolar size in all treated groups. After 30-day exp. + 120-day rec., LD M showed a dec'd (not stat. sig.) mean alveolar diameter, whereas MD M showed inc'd (not stat. sig.) mean alveolar diameter. F showed slightly inc'd alveolar diameter at the LD level and stat. sig. inc'd at the MD level. Alveolar size determination for the HD after 30-day exp. + 120-day rec. were not obtained due to deaths before scheduled necropsy. (See Appendix F for tabulated data.)

DNA Content of Lungs

Lab Performing Studies:

Proj. Rpt. No.:

Results

Mean DNA Analysis of Ferret Lung Tissue
Exposure Time of 30-days; Sacrifice at Termination

| Dose Level (ug/L) | Sex | Body Wt (g) | Protein (mg) | DNA (mg) | DNA/ Protein | DNA/ Body Wt |
|---|---|---|---|---|---|---|
| 0 | M | 240 | 133 | 24.4 | 0.18 | 0.10 |
| 0 | F | 206 | 98.2 | 18.9 | 0.20 | 0.10 |
| 162 | M | 216 | 131.7 | 22.7 | 0.18 | 0.12 |
| 162 | F | 152 | 81.0 | 14.8 | 0.18 | 0.11 |
| 355 | M | 109 | 71.9 | 16.2 | 0.24 | 0.15 |
| 355 | F | 84 | 53.9 | 12.5 | 0.23 | 0.15 |
| 620* | M & F | - | - | - | - | - |

*Data for these dose levels not obtained due to preterminal deaths.

Evaluation of data in the above table shows a highly sig. inc. in lung DNA content in the MD ribavirin exp. group. Animals of the HD group died preterminally.

Mean DNA Analysis of Ferret Lung Tissues
Recovery Animals

| Exp. Time (days) | Sac. Time (days) | Dose Level (ug/L) | Sex | Body Wt (g) | Protein (mg) | DNA (mg) | DNA/ Protein | DNA/ Body Wt |
|---|---|---|---|---|---|---|---|---|
| 10 | After | 0 | M | 1611 | 747 | 51.4 | 0.070 | 0.032 |
| | 140-day | 162 | M | 1548 | 851 | 51.9 | 0.062 | 0.035 |
| | recov. | 355* | M | - | - | - | - | - |
| | | 620* | M | - | - | - | - | - |
| 30 | After | 0 | M | 1578 | 797 | 53.0 | 0.068 | 0.033 |
| | 120-day | 0 | F | 813 | 453 | 33.3 | 0.074 | 0.041 |
| | recov. | 162 | M | 1434 | 887 | 54.2 | 0.060 | 0.037 |
| | | 162 | F | 840 | 471 | 33.8 | 0.072 | 0.040 |
| | | 355* | M & F | - | - | - | - | - |
| | | 620* | M & F | - | - | - | - | - |

*Date for these dose levels not obtained due to preterminal deaths.

Evaluation of the above table shows no difference between DNA/protein & DNA/body wt ratios between LD & controls. Animals of the MD & HD gps died preterminally.

SUMMARY

A. The ferret inhalation toxicity study submitted in this amendment was performed to determine the effect of Ribavirin aerosol on lung development in young animals. The study involved administration at whole body inhalation chamber exp. concentrations of 162, 355 & 620 ug/L (i.e., 60, 131 & 229 mg/kg/day approx. exp. doses) to jill ferrets and their litters for 6 hrs./day for 10 & 30 consecutive days, followed by 140 & 120-day rec. periods, respectively. Findings in kits included the following at both 10 & 30-day exp.: inc'd incidence of kit mortality & stat. sig. dec'd body wt gain in the MD & HD exp. gps, both considered by the applicant to be due to nutritional deficiency caused by MD & HD jill lactation failure.

Additional findings observed at the MD & HD levels consisted of generalized and local hair loss (30-day exp.), thin animals (10 & 30-day exp.), discolored livers, kidneys, & spleens (10 & 30-day exp.) and gastrointestinal toxicity (ulceration & hemorr. of gastric mucosa) at 30-day exp.

Lung pathology consisted of the following at interim kill: after 10-day exp., pulmonary hemorr. which, although seen at both control & drug-treated levels, was more severe (mild vs. minimal) in the LD & HD gps. In addition, alveolar histiocytosis was reported in 1/3 kits at the LD; according to the investigator this lesion had "similar genesis as the interstitial inflammation", reported in other parts of this study. After 10-day exp. + 20-day rec., interstit. pulmonary inflammation was inc'd in incidence at the LD & HD levels over controls (i.e., control = 1/3, LD & HD = 2/3 & 1/2 animals, respectively). In the 30-day exp. gp, an inc'd incidence of pulmonary interstit. inflammation was observed at the LD (2/6 vs. 1/5 in controls). Intercurrent deaths occurring in kits at the HD level also showed pulmonary interstit. inflammation. If these date are included in with the 30-day exposure data, the incidence of pulmonary interstit. inflammation at 30 days exp. is inc'd over controls, not only at the LD, but also at the HD levels (i.e., 1/3 animals at 11 days in the HD gp vs. 1/5 in controls).

Recovery animals showed the following at terminal kill of 10-day exp. animals after 140-days rec.: pulmonary interstit. inflammation & microlithiasis at the same incidence in both control & drug-treated gps; moderate pulmonary & liver congestion at the MD level. For terminal kill 30-day exp. animals after 120 days rec., no conclusion could be made with respect to the HD gp, as 50% of the animals died 10-25 days into treatment. As for the control, LD & MD gps, the incidence of pulmonary interstit. inflammation was the same for all 3 gps. There was, however, an inc'd incidence of foreign material & focal granulomatous inflammation at the MD level.

Jills exposed to ribavirin aerosol for 6 hrs/day for 10 & 30 days and sacrificed 5-26 days after 30-day exp. & 25 days after 10-day exp. showed the following: inflammation of the mammary glands in control & drug-treated gps at both exp. times; minimal pulmonary hemorr. & mild granulomatous inflammation in 10-day exp. jills at the LD & MD levels,

respectively; minimal pulmonary interstit. inflammation & mild hemorr. at the 30-day exp. level and mild pulmonary interstit. inflammation at the 30-day MD exp. level.

B. Pulmonary function studies were performed on ferrets. Kits were exposed to aerosol ribavirin. Pulmonary function data was obtained at 40 days of age (i.e., at weaning = 20 day-rec. after 10-day exp. in 10-day-old animals and after 30-day exp. in 10-day-old animals) and at maturity at 160 days of age (i.e., at 140-day rec. after 10-day exp. and at 120-day rec. after 30-day exp.). Results indicated the following: at 20-day rec. after 10-day exp., dec'd compliance, vital capacity measured during forced expiration, maximum expiratory flow at 50% of forced vital capacity, tidal & minute volume, and inc'd pulmonary resistance & respiratory rate at the HD level; dec'd compliance, maximum expiratory flow at 25 & 50% of forced vital capacity & respiratory rate, and inc'd pulmonary resistance at the LD level. At 140 days rec. after 10-day exp., the HD group still showed dec'd compliance & respiratory rate, accompanied by dec'd tidal & minute volume and inc'd pulmonary resistance; the adverse changes seen in the LD animals at 20-day rec. were reversed after 140-day rec. After 30 day exp., HD animals died before the scheduled test; consequently, no values were obtained. However, during this exp. period, LD M showed dec'd compliance, vital capacity measured during forced expiration and during slow-expiration, maximum expiratory flows at 25 & 50% of forced viral capacity, maximum static compliance, tidal & minute volume, and inc'd pulmonary resistance & respiration rate; other than the inc'd pulmonary resistance & respiratory rate, F were negative. At 120-day rec. after 30-day exp., LD M still showed dec'd compliance, FVC, maximum expiratory flow at 25 & 50% of forced vital capacity & tidal volume, and inc'd respiratory rate; F at the LD & MD levels showed dec'd compliance maximum expiratory flows at 25 & 50% of forced vital capacity, respiratory rate & minute volume and inc'd pulmonary resistance.

C. Lung lavage studies performed on these ribavirin-exposed ferret pups showed that the drug had an effect on the lavagable cell pool of the growing lung. This effect manifested itself as follows: dec'd no. of lavaged cells ("attributed to difference in lung weights within the different exposure groups") at the MD & HD after 10-day exp., at the LD & MD levels after 30-day exp., and in the LD M after 30-day exp. followed by 120-day rec. Dec'd cell viability occurred at the HD after 10-day exp., at the MD after 30-day exp., and in the LD (M) after 30-day exp. followed by 120-day rec. Peroxidase positive macrophages were inc'd in the HD group after 10-day exp., in the LD & MD groups after 30-day exp., and in the LD group after 10-day exp. followed by 140-day rec.

D. Morphometric analyses of the lungs showed a real dose-related enlargement of alveolar diameters at 40 days of age after exp. to ribavirin for either 10 or 30 days. This enlargement had disappeared in M by the age of puberty, but was still present in F at that time.

E. Analysis of 30-day ribavirin exposed ferret lungs for DNA content showed an increased DNA/protein ratio at the MD level, indicating "the possible presence of a mild proliferative response." DNA/body wt ratios showed a

highly significant increase at the mid dose level, which could be due to cell proliferation or to changes in cellular distribution." No effect on these parameters was seen in the LD group. Results at the HD level are unknown due to unavailability of data for this dose level.

## CONCLUSIONS

A. According to the applicant's proposed package insert, "using the recommended drug concentrations of 20mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 ug/liter or 190mg/$m^3$: the estimated exposure dose of human infants at 190mg/$m^2$ for 12 hours is about 10mg/kg/day."

A "no effect" dose level for pulmonary injury after inhalation exposure was not established in suckling ferrets exposed to ribavirin for 6 hrs/day for 10 & 30 days. The lowest dose tested in these animals (i.e., 60mg/kg/day) was 6x higher than the lowest dose proposed for use in the human infant (i.e., 10mg/kg/day) and 4x higher than the highest dose proposed for clinical use i.e., 15mg/kg/day). The daily duration of admin. in ferrets (6 hrs) was 2-3x shorter than the duration of admin. proposed for clinical use (i.e., 12-18 hrs/day). In these studies, ribavirin treated animals showed histopathological evidence of an increased incidence of lung injury [i.e., interstitial pulmonary inflammation & hemorrhage; these lesions are similar to, but less extensive than, those reported in 28-day ribavirin inhalation studies performed in rats & mice by , in which lower doses (22, 30 & 57mg/kg/day in rats; 30, 62 & 111mg/kg/day in mice) and a longer duration of exposure (12 hrs/day) was used. See my review of dated 4/17/84.] Changes were also observed in pulmonary function, cell viability, nos. of pulmonary macrophages, pulmonary alveolar size & DNA content of the lung.

The validity of the histopath. findings reported for control & drug-treated recovery animals at puberty is questioned. The applicant reports that "minor pulmonary lesions which were encountered included interstitial inflammation, microlithiasis, hemorrhage, congestion, foreign material & focal granulomatous inflammation and that all these were considered to be incidental findings or part of spontaneous disease complexes of ferrets. The incidence of these findings in controls was roughly equal to the incidence in exposed animals, thus there was no apparent compound associated lesions." It is noted that the applicant has submitted no documentation or historical background data to support their position that the pulmonary lesions observed in this experiment are due to part of spontaneous disease complexes in ferrets. In addition, their conclusion that "the incidence of these findings in controls was roughly equal to the incidence in exposed animals" is in error, as there was an increased incidence of pulmonary congestion in MD 10-day exposure animals at 140 days recovery and an increased incidence of foreign material & focal granulomatous inflammation in MD 30-day exposure animals at 120-day recovery, as compared to controls. Pulmonary function parameters were still altered in some recovery animals at puberty (i.e, HD 140-day rec. 10-day exposure and LD & MD 120-day recovery 30-day exposure animals) as

was cell viability (i.e., decreased in LD 10 & 30-day exposure, 140 & 120-day recovery animals, respectively) and alveolar size (i.e., increased in HD 30-day exposure 120-day recovery animals).

2. Generally, the dose recommended for use clinically is a fraction of the "no effect" dose level found in the most sensitive species. Inasmuch as "no effect" levels for inhalation toxicity were established in neither the present nor any past preclinical study submitted by Viratek, a recommendation of an appropriate (safe) dose for clinical use in infants cannot be based on available preclinical studies.

RECOMMENDATION

The results of this study do not cause me to change the recommendation reached in my review of the ribavirin aerosol NDA #18-859, dated 3/26/84.

Norma J. Browder

Norma J. Browder, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/NJBrowder/smc/7/1/85
R/d init.by:JMDavitt
3918b

APPENDICES ATTACHED

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 18-859 (Amendment dated September 17, 1984 - Labeling Review)

Date Review Completed: May 31, 1985

Sponsor: Viratek

Drug: Ribavirin (Virazole) Aerosal

Comments:

A) Viratek's labeling for Ribavirin aerosal was submitted in an amendment to their NDA dated September 17, 1984.

B) During the week of 5/6/85, a request was received from the CSO asking pharmacology to evaluate and make revisions in the sponsor's submitted labeling.

C) The labeling as submitted is unsatisfactory. Approval of the labeling as submitted is not recommended.

D) Approval of this application by the assigned medical officer will require the following recommended revisions in the preclinical pharmacology sections of the label:

1) The section entitled "Other Pharmacological Studies" should be relabeled to read "Animal Pharmacology and Toxicology".

2) The sections entitled "CNS and Autonomic Activity" and "Cardiovascular and Respiratory Activity" should be under the "Animal Pharmacology and Toxicology" section. These sections as written should be deleted because they do not accurately reflect the actual data submitted. Under the "Cardiovascular and Respiratory Activity" section, the statement should read to reflect the following: An IV dose of 1 mg/kg followed after 35 minutes by a 70 mg/kg IV dose caused no significant change in blood pressure, heart rate or respiratory rate. A 30 mg/kg single dose IV injection produced immediate but transient increase in both blood pressure and heart rate persisting for 2 minutes. Slow IV infusion to a total dose of 30 mg/kg at a rate of 0.8 mg/kg/min., over 38 minutes, produced no significant change in blood pressure or heart rate, but an increase in respiratory rate during the 10-25 minute infusion period. Blood pressure elevations produced by epinephrine, norepinephrine, tyramine & angiotensin were increased after slow infusion of virazole.

3) Under the CNS and Autonomic Activity section the statement as presented in the sponsor's package insert should be deleted. Pharmacology has reviewed all data submitted to the Agency to date on ribavirin and has been unable to find any studies which were designed to detect the drug's effect on neurological function or its ability to induce benavioral toxicity.

4) Under the section entitled "Immunological Effects," the statement as written should be revised to reflect the following: Immunological studies performed using ribavirin showed that ribavirin was not an immunosuppressant agent in terms of humoral immunity in man, rats, mice and rabbits. The drug however, did show show immunosuppressant activity in terms of humoral immunity in guinea pigs and ferrets when used at doses of 100 mg/kg/day or greater. Celluloid immunity models indicated that ribavirin had a mild immunosuppressant effect at a conc'n of 50 mg/kg/day and above.

5) Under the section entitled "Pharmacokinetics -- Distribution", the statement now present in the label should be revised to accurately reflect the concentration of drug in the RBC's of the human. According to the medical officer's review of NDA 18-266 dated August 10, 1979 (Dr. J. Canchola), results of one clinical study showed that administration of a single oral dose resulted in "two peak drug plasma levels detected at 1 & 24 hours after administration. Drug plasma conc'n showed two phases with half lives of 15 & 24 hours respectively. Inspection of the drug plasma levels showed that the DPM counts progressively decreased in the plasma and increased in the RBC's from 1 hour to 195 hours post-dosing (last sample) with a RBC/plasma ratio equal to 42 at 81 hours, and ratio equal to 80 at 195 hours."

The statement should also include that the drug is sequestered in the RBC's of rats after IM dosing and in rhesus monkeys after IV and IM dosing and was still present in the RBC's of rats after 3 days and in the RBC's of monkeys after 43 days with IM dosing and after 36 days with IV dosing.

5) The section entitled "Excretion and Metabolism" needs to be revised. There are discrepancies in the values for recovery noted in baboons and rats reported in the sponsor's label as compared to the values reported in their submissions. It would be more accurate to state that absorption, distribution and excretion studies performed in rats, monkeys, dogs and baboons using radiolabeled drug showed urinary excretion to be the major route of elimination with drug still being recovered at 96 hours in the monkey, dog and baboon and at 72 hours in the rat.

7) Under the "Animal Pharmacology and Toxicology" section a summary of the toxicities seen in oral and inhalation toxicity studies should be stated to reflect that to date the major toxicities reported for Ribavirin in subacute and chronic oral preclinical animal studies consisted of dose-related deaths, anorexia, wt loss, diarrhea, GI toxicity, depression of hematological parameters, bone marrow atrophy, lymphoid atrophy of the thymus, spleen and lymph nodes, hepatotoxicity, myocarditis, nephritis, retinal degeneration, testicular atrophy and accumulation of fluid in the subcutis, body cavities and various organs.

The major toxicities reported for ribavirin in subacute inhalation preclinical studies consisted of increases in respiration rate, depression of hematological parameters, hepatotoxicity,

myocarditis associated with myofiber necrosis and interstitial edema, multifocal mineralization of the heart, pancreatitis, kidney toxicity, mortality, weight loss, dehydration, pulmonary alveolar edema, hemorrhage & adematosis, thymus atrophy, hypocellular bone marrow, GI enteropathy and necrosis of the head skeletal muscles.

8) Under the section entitled "Carcinogenicity Studies," the entire section as written by the sponsor should be deleted. This section should be relabeled and entitled "Carcinogenesis, Mutagenesis and Impairment of Fertility" and should read to reflect the following: Carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that in the rat, chronic feeding of ribavirin at dose levels in the range of 22-95 mg/kg body weight can induce an increase in benign mammary and pituitary tumor incidence among ribavirin-treated animals. In the same studies, there was an increased incidence of benign pancreatic tumors and an increase in the incidence of adrenal pheochromocytoma at dose levels in the range of 33-70 mg/kg. Results of long term parenteral administration to scrapie-infected mice do not indicate a tumorigenic response, but the number of animals and the dosage regimen (i.e., 2x/week) used in this study was insufficient to support a conclusion with respect to oncogenicity potential. The oncogenic potential of ribavirin in rodents should be further evaluated in repeat ongoing carcinogenicity studies.

   The reference that the sponsor makes to the 6 month IBT monkey studies in which doses of 30, 60 and 120 mg/kg were used, should be deleted from the carcinogenicity section of the label because (1) it was not a carcinogencity study and (2) it does not accurately reflect the toxicities which were reported for that study. Reference to the actual toxicity observed in this study is included under my recommendations for the revised animal toxicology portion of this label (see Animal Pharmacology and Toxicology section of this review).

9) The sponsor's section of the label referring to the results obtained in cell transformation studies should be deleted and revised to reflect the following: In the Balb/3T3 in vitro mouse cell transformation assay, used to provide preliminary assessment of potential oncogenicity in advance of more definitive life-time bioassays in rodents, ribavirin was positive at a dose of 15.0 ug/ml in two independent trials. This section should be included under the "Carcinogenesis, Mutagenesis and Impairment of Fertility" section.

10) The sponsor's section of the label referring to the results obtained in mutagenicity studies should be deleted and revised to reflect the following:

   a) In a mammalian cell assay (L51784 mouse lymphoma cells in vitro) ribavirin produced a positive response for mutagenicity. The drug was negative for mutagenicity in the mouse dominant lethal, rat host mediated, Ames and Rosenkranz polymerase assays.

b) In vitro cytogenetic assays performed in human leucocytes and rat fibroblasts were negative for chromosome abnormalities. In addition, ribavirin was negative in an in vitro cytogenetic test system utilizing rat bone marrow cells.

c) In the Drosophila sex-linked recessive test, ribavirin showed a drug-induced killing of germ cells at or near the time of meiosis (spermatocytes). This effect manifested itself in that treated males were almost completely sterile in brood three. Those not 100% sterile showed an extreme reduction in productivity.

These sections should be included under the "Carcinogenesis, Mutagenesis and Impairment of Fertility" section.

11) In the next section of the sponsor's label entitled "Immunosuppressive Studies", the preclinical animal studies which are referenced should be deleted, since they are dealt with under the section labeled "Immunological Effects."

12) Pregnancy Category: The sponsor has listed the correct pregnancy category in the label as being Category C. However, the statement as written by the sponsor needs to be revised. The sponsor's statement referring to the studies performed in subhuman primates should be deleted for the following reasons:

a) Inadequate design of study. The drug was not given during the entire period of organogenesis (i.e., 20-45 days) as required by FDA reproduction guidelines. Drug was given only for 4 days in each animal (i.e., days 20-23, 24-27, 28-31, 32-35 and 36-39).

The revised pregnancy statement should read to reflect that ribavirin was teratogenic in rats at oral doses as low as 10 mg/kg, embryolethal in rabbits at 1.0 mg/kg, induced fetal deaths & congenital anomalies at IP doses of 1.25 mg/kg in the hamster and resorption and tetratogenicity at IP doses of 50-150 mg/kg in mice when administered during organogenesis. The sponsor should delete their statement that reads, "Outside of this critical period, no teratogenicity or embryocidal effects have been observe in these animal species."

13) Under the "Adverse Reactions" section, the statement referring to the drug-induced anemia occuring in monkeys as being clinically insignificant should be deleted.

In addition, the sponsor's claim in the 2nd paragraph under adverse reactions, relating that accumulated data on the anemia seen in normal human subjects receiving oral ribavirin is mild, should be revised.

s. In addition, according to the division's memo of 8/8/83, addressed to the Acting Director, Office of NDE, "there is clinical evidence of hemolytic anemia and suggestive evidence of bone marrow suppression" connected with ribavirin administration.

Norma J. Browder, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/NJBrowder/smc/6/28/85
R/d init.by:JMDavitt
4247b

8/5 file

# REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 18-859 (Amendment dated 6/18/85)

Date Review Completed: 6/24/85

Applicant: Viratek

Drug: Virazole (ribavirin) Aerosol

Comments:

A. Labeling for ribavirin aerosol has been submitted in this amendment.

B. After discussion and concurrence with the medical officer on 6/21/85, it was decided that the following revisions should be made in the labeling before approval:

1. Under "Warnings" and in the boxed warnings sections, the following statement should be added: "In rats, mice and monkeys, ribavirin administration resulted in cardiac lesions. The significance of these findings to human administration is unknown."

2. In the "Adverse Reactions" section, the second sentence in the first paragraph should be changed to read: "In infants, ribavirin aerosol use has rarely been associated with worsening of signs of respiratory tract disease, pneumothorax and rash. Reticulocytosis has been observed in infants, but the frequency is not known. Monkeys administered 30mg/kg/day or more of ribavirin for 10 days showed a reduction of red blood cell counts, hematocrit and hemoglobin during treatment; reticulocytosis was observed 12 days after treatment was stopped."

3. MORS's #5, 10 & 11 refer to adverse reactions or events "which are associated with ribavirin use and cannot be attributed to other causes with certainty," and are therefore possibly related to ribavirin. It is recommended that a summary of these findings be incorporated into the "Adverse Reactions" section.

4. The "Adverse Reactions" section currently states: "Anemia, which occurs frequently with oral and intravenous ribavirin, has not been shown to be associated with use of the aerosol." It is noted that the MOR for the oral formulation reports several clinical instances in which anemia was not detected until a number of days after initiation of treatment. The reported absence of anemia in association with use of the aerosol may be due to the fact that the duration of follow-up in patients receiving the aerosol was inadequate to detect anemia. It would probably be more accurate if this section of the labeling were revised to read as follows: "Anemia, which occurs frequently with oral and intravenous ribavirin has not been adequately studied during the appropriate follow-up periods in patients receiving the aerosol."

C. This amendment also contains studies for two oral feeding carcinogenicity protocols. After review of these protocols, the following recommendations are made: Agency policy calls for carcinogenicity studies in two species. It is not clear whether Viratek plans to do these studies in two species, or a single study in one species. It is recommended that the studies employ two species. One of these studies should be performed by the oral route (via gavage), with some animals allocated for plasma level determinations. The other should be done using inhalation or intratracheal instillation.

D. The following additional preclinical studies have been recommended for performance post-marketing:

1. "Study of physical-chemical and pharmacologic interactions of ribavirin with digoxin, aminophylline, other bronchodilators and antibiotics." (See MOR #12 dated 4/25/85.)

2. Study of drug-induced toxicity in neonatal animals. These studies were requested in our letter to Viratek dated 9/3/83.

3. Study of drug disposition, retention & clearance as well as systemic exposure (blood & urine levels) following inhalation. These studies were requested in the pharmacology review of the aerosol NDA dated 3/26/84, in a memo of telcon with Viratek dated 12/19/83 and in our 9/3/83 letter to Viratek, re:

Norma J. Browder, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/NJBrowder/smc/7/26/85
R/d init.by:JMDavitt
0015p

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 18-859 (Original Submission)

Date Review Completed: 3/26/84

Applicant: Viratek

Drug: Ribavirin (virazole)

Category: Antiviral (aerosol)

Formulation: Supplied as a sterile, lyophilized powder. Each vial contains 6 grams of ribavirin, which when reconstituted to recommended volume of 300ml with water for injection, will contain 20mg of drug/ml of solution.

Proposed Indications: Indicated in the treatment of respiratory syncytial virus (RSV) infections in infants.

Dosage & Route of Administration: According to the applicant's package insert, "using the recommended drug conc'n of 20mg/ml ribavirin as the starting sol'n in the drug reservoir of the SPAG unit, the average aerosol conc'n for a 12-hr period would be 190ug/liter (0.19mg/l) of air. The pulmonary retention factor has been demonstrated to be 0.75. A normal adult will retain 70% of the aerosolized ribavirin. This will provide a retained dose of 50-55mg/hr of exposure. The usual dose is based on exposure to the aerosol 12-18 hrs/day for 3-5 days. The aerosol dose will vary by minute volume & body wt. A safe upper limit for humans has not been established as no adverse effects have been observed in clinical trials."

Related Submission

Toxicity Studies

A. Background information on previously performed preclinical studies can be found by reference to pharm. reviews.

B. Additional mutagenicity and cell transformation studies were reported by Viratek in the present NDA for the aerosol on 3/21/82. The aerosol NDA was not filed at that time; however, a review & evaluation of the mutagenicity & cell transformation data was completed on 7/29/83. Background information on these data can be obtained by reference to my pharm. review of NDA 18-859 dated 7/29/83.

C. Preclinical studies submitted in the aerosol NDA which have not been reviewed in connection with previous submissions consist of the following:

1. Acute inhalation squirrel monkey studies;

2. 28-day oral toxicity study in rats.

Evaluation of All Unreviewed Data
Submitted to NDA 13-859

Abbreviations to be used:

| | | |
|---|---|---|
| C = controls | dec = decrease(d) | DT = drug-treated |
| LD = low dose | inc = increase(d) | DR = drug-related |
| MD = mid dose | sig = significant | PD = post-dosing |
| HD = high dose | SS = statistically significant | PT = pretest |

A. Acute Inhalation Toxicology: Squirrel Monkeys

Lab Performing Study: Aerobiology, Div. of U.S. Army Med. Research Inst. of Infectious Diseases (USAMRIID), Ft. Detrick, Frederick, MD

Conditions of Study Conduct: Completed prior to implementation of GLP regulations.

Material Tested: Ribavirin (Lots #1229-29, 1975 & #1229-39, 1977) dissolved in distilled water. Controls received sterile distilled water in an aerosol.

Species & Sex: M & F squirrel monkeys (Saimiri sciureus) weighing between 380 & 810 g on study day zero.

Exposure Apparatus: Same as that described by Berendt et al. (1977), except cages described were replaced by a plexiglas chamber (32x25x40 cm) capable of exposing 4 monkeys simultaneously. Exposure chamber was fitted with perches, trays for food & water, and collection of waste. System allowed continuous exposure to aerosol.

Study 1: Pilot Study

Dose Levels: controls (water aerosol); test group (40mg/kg/day ribavirin aerosol

Route & [illegible]ation: inhalation; 22 continuous hrs/day for 4 days

# Animals: 4 in the control gp; 8 in the test gp

Parameters Evaluated: food intake, body wt & temp, RR, general activity, sneezing/coughing; measurements made on test days 1, 5, 9 & 25 (no 25-day measurement in controls); hematology (Hct Hb, RBC, total WBC, reticulocytes, MCV, MCH & MCHC), beta glucuronidase, gross necropsy, histopath. & organ wts not recorded.

Sacrifice: 2 monkeys from C and 4 from DT gp killed 0 hrs after last exposure; remaining animals (2 from C & 4 from DT gp) killed 30 days after last exposure.

Results

Clinical Observations: (1) Body wts were within normal limits throughout study; greater than PT values by study termination for ribavirin treated monkeys. (2) Rectal temp & appetite showed no DR effects. (3) RR was elevated on days 1, 5 & 9 in C & DT animals on days 1, 3 & 25.

Clinical Pathology: Hematology: in DT gp & C: dec in Hct, Hb & RBC in both gps from days 1-9 - greater in DT than C gp. By day 25, Hct, Hb & RBC in DT gps were still dec, but were approaching PT levels; dec in WBC in DT gp on days 1 & 5, then inc to 2x PT level on day 9; WBC was still dec but approaching PT level on day 25; dec in MCV, MCHC & MCH in DT gp during treatment (reaching lowest level on day 5); MCV & MCH still dec on day 25; inc in reticulocytes on day 3 & continuing until day 25 in DT gp.

*Control animals had no measurements on day 25.

Clinical Chemistry: The DT gp showed a moderate inc in beta glucuronidase on days 1 & 9 (indicating liver toxicity). By day 25 values were slightly depressed but returning to PT values.

Gross & Microscopic Pathology:

- Liver: DT gp: subacute centrilobular fatty metamorphosis in monkeys sac'd immediately after dosing (severe in 2/4 & moderate in 1/4); minimal subacute suppurative, multifocal hepatitis in 1/4 sac'd immed. PD and in 1/4 sac'd 30 days PD; moderate diffuse karyomegaly of the hepatocytes in 1/4, and acute diffuse degeneration in 1/4, sac'd immed. PD. Controls: minimal hepatitis in 2/2 sac'd immed. PD
- Kidney: DT gp: Animals sacrificed immed. PD - slight to mod. fatty metamorphosis of tubular epithelium in 1/4; mod. fatty metamorphosis of the distal convoluted tubule in another 1/4; mod. acute cloudy swelling of convoluted tubules in 2/4 (multifocal in 1). Animals sac'd 30 days PD - minimal fatty metamorphosis in 1/4.
- Lymph Node: hemosiderosis in 1/4 sac'd 30 days PD in DT gp.
- Heart: myocarditis in 1/4 sac'd 30 days PD.
- Pancreas: pancreatitis in 1/4 sac'd 30 days PD.

Study 2: 5-day Toxicity Studies

Dose & Route: Gp 1 - controls (water aerosol); Gp 2 - ribavirin aerosol, 40mg/kg/day; Gp 3 - ribavirin IM, 40mg/kg/day*; Gp 4 - ribavirin oral, 40mg/kg/day*; Gp 5 - water IM, 0.4ml; Gp 6 - water PO, 0.4ml

*100mg/ml sol'ns of drug in distilled water; all animals received 0.4ml/treatment.

Duration: Gps 1 & 2, 2.5 hrs in morning & 2.5 hrs in afternoon; all monkeys treated for 5 days.

# Animals: 4/group

Parameters Evaluated: Baseline obs. on study days -7, -5 & -3 for gps 1-4 & on day -3 for gps 5 & 6. Test observ. days 0, 1, 2, 3, 4 & 7 for gps 2-4 and days 0, 1, 2, 3 & 4 for gps 1, 5 & 6. Observ. included food intake, RR, body wt & temp, general activity, nasal secretions, sneezing/coughing, dyspnea, hematology [Hct, RBC, Hb, platelet ct, reticulocyte ct, WBC, differential WBC (neutrophil & lymphocyte cts), MCV, MCH, MCHC], serum chemistry (BUN, alkaline phosphatase, total & direct bilirubin, total protein albumin, CPK, LDH, SGPT & SGOT].

Sacrifice: Animals were not killed at the end of the obs. period; consequently, no organs or tissues were available for evaluation.

Results

Clinical Observations:

- Group 1 vs. Group 2: According to the applicant, "no changes of biological or statistical significance were found in treated animals over the course of the study when compared to controls for the following: food consumption & body wt." No change in RR or body temp was noted between control & DT gps. Slight dec in activity (-1) in 3/4 DT animals vs. controls (+2). Dyspnea in 2/4 DT animals (days 1 & 2 PD). Nasal secretions observed in 3/4 after dosing on exposure day 0 and during exposure on days 1-3; according to the applicant, these animals "had white crust around the nostrils post-exposure on day 0 & during exposure on day 1." The remaining animal had nasal secretions during exposure on days 1-3 ("white crusting only on day 1 during exposure".) Sneezing occurred in 1/4 animals during the first 4 days of exposure.

- Group 5 vs. Group 3 & Group 6 vs. Group 4: No DR signs of toxicity seen.

Hematology:

- Gp 1 vs. Gp 2: Dec in Hb & RBC in both C & DT animals - greater in DT; both C & DT animals showed increases in reticulocytes beginning during the PT period ("DT treated monkeys had delayed responses in the regeneration process, 3 to 4 days."); dec in WBC in both C & DT - greater in DT; general [illegible] in segmented neutrophils in DT.

- Gp 5 vs. Gp 3: Dec in Hb, Hct & RBC in both C & DT gps - greater in DT; inc in reticulocytes in both C & DT ("max inc day 3 in controls vs. day 4 in drug treated; therefore regeneration slightly delayed in drug treated").

- Gp 6 vs. Gp 4: Dec in Hct, Hb & RBC in both DT & C (less in DT than in controls). "Both groups had increases in reticulocytes."

Clinical Chemistry:

- Gp 1 vs. Gp 2: No DR changes

- Gp 5 vs. Gp 3: Elevated BUN on day 7 in DT gp.

- Gp 6 vs. Gp 4: Elevations in SGOT, SGPT & LDH (indicative of possible liver impairment) and inc in BUN in DT gp.

Study 3: 4-Day Toxicity Studies

Dose & Route: Gp 7 - ribavirin PO, 400mg/kg/day; Gp 8 - ribavirin PO, 40mg/kg/day; Gp 9 - water aerosol; Gp 10 - ribavirin aerosol, 40mg/kg/day

# Animals: 6/group

Duration: 4 days; Gp 10 monkeys exposed to aerosol 2.5 hrs in morning & 2.5 hrs in afternoon

Formulations Tested: Gps 7 & 8, 100mg/ml of drug in sterile distilled water (Gp 7, 4ml/treatment and Gp 8, 0.4ml/treatment)

Parameters Evaluated: Baseline obs. made on days -3, -6 & -4 for all gps and days 1, 3 & 6 for test gps. Observ. made were the same as those in study #2; hematology tests were for Hct, RBC, Hb, RI & erythrocyte indices; clinical chem. included SGPT, [illegible] & LDH.

Sacrifice: Monkeys were not killed at the end of obs. period; consequently no organs or tissues were available for evaluation.

Results

Clinical Observations:

- Gp 9 vs. Gp 10: No DR effects seen on body wt or temp; inc in RR for DT gp vs. C during exposure; dec in activity in DT animals over C (+1 vs. +2 for C); dyspnea seen in 1/6 DT monkeys on days 3 & 4.

- Gp 8 vs. Gp 7: According to the applicant, food intake was dec in both DT gps during treatment; animals were eating normally by the end of the obs. period; dyspnea was observed in 1/6 monkeys on all treatment days at 40mg/kg; at 400mg/kg, dyspnea was observed in all animals on one or more treatment days; dec activity was also observed in all monkeys in both DT gps.

Hematology:

- Gp 9 vs. Gp 10: Dec in Hct, Hb, RBC & WBC in both C & DT gps; DT animals did not appear to be more affected than C.

- Gp 8 vs. Gp 7: At 400mg/kg: Dec in RBC, Hct & Hb (approx. 40% over PT levels); slight dec in WBC. Animals at 40mg/kg showed no sig. diff. in these parameters when compared to PT levels. Reticulocyte cts & platelet values were not taken for this gp.

Clinical Chemistry:

- Gp 9 vs. Gp 10: According to the applicant, no DR changes were observed. Actual data were not submitted.

- Gp 8 vs. Gp 7: No actual data were submitted; however, according to the applicant, "monkeys given 400mg/kg/day had slight elevations in LDH on day 6. No drug-related effects were seen in SGOT or SGPT values in either drug-treated group or in LDH in the 40mg/kg group."

Conclusion: Refer to Summary & Evaluation, "Subacute Toxicity Studies".

B. 28-Day Toxicity Study: Rat

Lab Perf. Study:

Proj. Rpt. No.:

Contract No.: DAMD 17-80-C-0161; study performed for & submitted to USAMRIID, Fort Detrick MD.

Material Tested: Ribavirin dissolved in 0.2% methylcellulose and 0.4% Tween 80 in sterile water for injection; controls received 0.2% methylcellulose, and 0.4% Tween 80 in sterile water.

Dose Levels Tested: Test sol'ns at conc'n of 30, 60 & 120mg/ml (i.e., 30, 60 & 120mg/kg/day).

Route & Duration: Oral intubation for 28 days

Species, Sex & # of Animals: M & F CR albino rats; 10/sex/gp

Parameters Evaluated: mortality, morbunidity, body wt, food intake, hematology, clinical chemistry, organ/body wt ratio, gross & histopath.

Results

Mortality: No DR deaths

Body Wts: Dec in mean body wt in M at MD & HD (not SS) and F (SS).

Food Intake: Dec in mean food intake at MD & HD levels each week.

Hematology:

- Decreases: mean Hct in HD M (days 14 & 29) and at all dose levels of DT F (days 14 & 29) - SS for day 14 mean for HD F & day 29 mean for HD M; mean Hb in HD M (SS on day 29) and all doses in DT F on days 14 (SS in HD F) & 29 (SS in HD F); mean erythrocyte counts in HD M (SS on day 29) and F at all DT levels on days 14 & 29 (SS in HD F on day 29); MRC in M on day 14 at all DT levels and on day 29 at the LD & HD levels; MRC in F at HD & HD and in M at all doses on day 29; SS in MCH in F at 30 & 60mg/kg on days 14 & 29; SS in reticulocyte ct in LD M on day 29.

- Increases: platelet counts in M at all doses on days 14 & 29 (sig. in HD M); platelet counts in F at all doses on day 29 (sig. at the HD level) and in F at the HD on day 14.

Clinical Chemistry:

- Decreases: alkaline phosphatase in M & F at all levels; SGPT in HD M & F and HD F; haptoglobin in M at all doses; LDh in HD & HD M & F.

- Increases: BUN in M & F at all dose levels (sig. in HD M); glucose in M & F at all dose levels (sig. in HD M); SGOT in M & F at all dose levels; CPK in LD & HD M and HD & HD F.

Gross Necropsy: thymus - small in 3/10 HD M and 1/10 HD F; testes - small in 2/10 HD M.

Organ Weight:

| | Mean Weight | | | Organ/Body Wt Ratio | | |
|---|---|---|---|---|---|---|
| | LD | HD | HD | LD | HD | HD |
| Males | | | | | | |
| Thyroid | dec | dec* | dec | dec | dec* | dec |
| Adrenal | inc | inc | inc* | inc | inc | inc* |
| Heart | | inc | inc | | inc | inc |
| Spleen | dec | dec | dec | dec | dec | dec |
| Kidney | dec | dec | dec* | dec | dec | dec* |
| Testes | dec | dec | dec | dec | | |
| Females | | | | | | |
| Adrenal | | | inc* | | | inc* |
| Spleen | dec | dec | dec | dec | dec | dec |

*statistically significant

Histopathology: (All dose levels represent mg/kg.)

- Thymus: congestion - 1/10 M at 60; lymphoid depletion - slight to mod. in 8/10 M & 7/10 F at 120. "Depletion was characterized by decreased numbers of small lymphocytes in the cortex." No changes were noted in controls (C).

- Heart: focal nonsuppurative myocarditis - 3/10 M & 3/10 F (minimal) at 120 and 4/10 C M

- Kidney: focal nephropathy - 4/10 C M & 6/10 C F (not remarkable) and 8/10 M & 3/10 F at 120 (min. to slight); regenerative tubular epithelium - 6/10 C M, 4/10 C F, 8/10 M & 3/10 F at 120; mononuclear inflammatory infiltrate - 5/10 C M, 3/10 C F, 9/10 M & 4/10 F at 120; unilateral dilation of renal pelvis - 2/10 M & 1/10 F at 120; cortical cysts - 1/10 M at 120

- Testes with Epididymis: perivascular mononuclear infiltrate in epididymis - 8/10 C M & 5/10 M at 120; unilateral hypospermatogenesis 1/10 M at 120 (mod.); bilateral hypospermatogenesis - 1/10 M at 120 (mod.-severe)

- Thyroid: hyperplasia in 1/10 F at 120

- Esophagus: muscle fiber degeneration - 3/10 F at 120 & 1/10 C F; mononuclear infiltrate: 3/10 F at 120 & 1/10 C F

Conclusion: Refer to Summary of Evaluation, "Acute Toxicity Studies".

## SUMMARY & EVALUATION

A. Virazole is a synthetic nucleoside, chemically known as 1-B-D-Ribofuranosyl -1, 2, 4-triazole-3-carboxamide.

B. According to published data, Virazole shows in vitro and in vivo antiviral activity against a wide range of both DNA & RNA-containing viruses.

C. Virazole is thought to evoke its antiviral activity after phosphorylation to its 5'mono,di and triphosphate analogs. The analogs then exert their antiviral activities in the following manner:

1. Virazole 5'-monophosphate is an inhibitor of inosine monophosphate (IMP) dehydrogenase.

2. Virazole 5'-triphosphate inhibits influenza A RNA polymerase and is also a potent inhibitor of the guanylation reaction in the formation of the 5'-Cap of mRNA.

D. Preclinical toxicity studies involving Virazole have been performed by the following 3 toxicology testing laboratories:

, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID),

E. The number of preclinical studies submitted by the above laboratories in support of Virazole total 54. Reviews and evaluations of all these studies have been completed and can be found by reference to the studies reviewed in connection with this NDA, as well as to the specific documents noted earlier in my review of this NDA.

F. The following comprises the toxicological profile on Virazole:

1. Acute Toxicity Studies: The acute oral toxicity of Virazole is 4-5gm/kg in the rat and 2gm in the mouse. Hypoactivity and signs of GI toxicity comprised the symptomatology observed. Monkeys treated acutely with doses as high as 10mg/kg showed no mortality. Adverse reactions consisted of diarrhea and vomiting.

2. Subacute Toxicity Studies:

Toxicological Resources: Admin. of Virazole in 45-day rat oral toxicity studies at doses of 60 & 120mg/kg produced a mortality rate of 30 & 60%, respectively, during the 3rd & 4th week of dosing. The 320mg/kg/day dose level produced a mortality rate of 60% within one week & 80% by the end of the 3rd week. Body wt loss, listlessness & occasional diarrhea were noted prior to death. Hematology, clinical chemistry and pathology findings were not reported.

Toxicological Resources: Daily IP doses of 90 & 180mg/kg, when administered for 30 days to rats, produced a 70% mortality rate from 8-15 & from 8-16 days, respectively. Admin. of 45mg/kg/day IP produced a 100% mortality rate from the 12th to the 21st day of dosing. Wt loss and lechargy were noted prior to death. Adhesions of the intestines were noted in all DT animals. Hematology, clinical chemistry & pathological findings (other than the intestinal adhesions) were not reported.

Toxicological Resources: Dogs treated with 40mg/kg/day of Virazole (oral, via capsule) for 30 days had reduced food intake throughout the study, a marked dec in body wt (stabilized after 2 wks treatment) emesis and diarrhea (from day 7 throughout study). Higher doses (150mg/kg/day for 3 days, 320mg/kg/day for 5 days & 90mg/kg/day for 21 days) administered to dogs produced lethals, preceded by loss of appetite and wt, and emesis & diarrhea from day 2 throughout the study.

Rats treated orally with Virazole for 28 days at doses of 30, 60 & 90mg/kg/day showed a sig reduction in body wt gain & food intake at 90mg/kg. 90mg/kg also resulted in a sig elevation in the bone marrow myeloid/erythroid ratio.

Virazole admin. orally at 200mg/kg/day for 30 days in rats produced an 80% mortality rate, a sig reduction in bod, wt, emaciation & diarrhea, a sig dec in mean corpuscular Hb & mean corpusc. conc'n in F, a sig dec in erythrocyte cts in M and a sig dec in Hb conc'n & Hct values in M & F. An inc in bone marrow M/E ratios was also observed.

Rhesus monkeys dosed orally at 30, 60 & 90mg/kg of Virazole for 30 days showed no drug-induced toxic effects; at 300mg/kg/day for 30 days, they showed a sig reduction in body wt, a sig erythrocytopenia and depression in Hct & Hb conc'n. Bone marrow exams showed a trend toward erythroid depression & 66% of animals (4/6) had myeloid/ erythroid ratios which were noticeably elevated over control values.

Rhesus monkeys dosed at 200mg/kg/day of Virazole orally for 30 days (with hematological parameters being followed through day 90) showed a sig reduction in the circulating erythrocyte population, Hct & Hb conc'n. Erythrocytopenia was progressive and a sig depression occurred by the 3rd day of dosing. The dec in erythrocytes was reversed after drug dosing was stopped (30 days). Normal counts existed by day 61. Bone marrow exam showed erythropoietic depression during dosing and a stimulation of erythrocyte production following drug withdrawal.

Baboons dosed orally with virazole (via injection in a banana) in 2 phases (Phase I, 135mg/kg/day for 7 days, inc to 203mg/kg/day for 7 days, inc to 303mg/kg/day from day 15-23; phase II, 303mg/kg/day for 21 days) showed a dec in body wt, Hb, RBC, PCV, mean corpuscular Hb, WBC cts & SGOT values at doses as low as 135mg/kg/day for 7 days.

Admin. of virazole in the diet of rats at doses of 154 & 185mg/kg/day for up to 2 days and at a dose of 500mg/kg/day via gavage for 1-3 wks, produced a dec in food intake and body wt until the 14th-19th day, elevated SGOT & BUN values, a reduction in RBC, Hb, leukocytes, reticulocytes & PCV, a 25-50% mortality rate, fluid accumulation in the SC tissues, thoracic & abdominal cavities, pancreas, lymph nodes & large intestines, bone marrow atrophy (myeloid & erythroid), lymphoid atrophy of the thymus, spleen & lymph nodes, multifocal coagulation necrosis of the liver and acute & subacute myocarditis.

Admin. of virazole via gavage to rats at doses of 30, 90, 120 & 200mg/kg/day, 7 days/wk for 4 wks, caused drug-induced deaths at doses as low as 90mg/kg, a dec in food intake & body wt, clinical chemistry changes indicative of a drug effect on liver & kidney and a dec in Hct, Hb & erythrocyte counts. Retinal degeneration was seen in animals at the 30 & 200mg/kg dose levels. Gross pathology showed accumulation of fluid in the abdominal & thoracic cavity at 120 & 200mg/kg. Microscopically, there was an inc incidence of foreign body pneumonitis, myocarditis, epicarditis, lymphocytic seminal vesiculitis and a dec in bone marrow cellularity at the 200mg/kg dose.

USAMRIID: Admin. of ribavirin IM at 30 or 100mg/kg/day for 10 days to rhesus monkeys induced a normochromic, normocytic, hypoproliferative dose-related anemia. This anemia was characterized by a decrease in circulating red cell mass, no change in erythrocyte indices and the absence of reticulocytosis during the treatment period. The developing anemia was accompanied by the absence of compensatory erythroid hyperplasia in the bone marrow of the LD group and erythroid hypoplasia in the bone marrow of the HD gp. Toxic effects on bone marrow were suggested by vacuolization of the red cell precursors, occasional vacuolization of other types of precursor cells and phagocytosis of red cells and red cell precursors by marrow histiocytes on day 10. Differential counts of cells in bone marrow indicated that ribavirin affected late ratio than early erythroid precursors. This suggests

that erythroid stem cells were unaffected and that the anemia was due, at least in part, to impaired red cell maturation."

Previous work (Ferrara et al., Antimicrobial Agents & Chemotherapy 19: (6), 1048-1049, June, 1981) "has shown that erythrocytes in rhesus monkeys accumulate ribavirin during treatment". In the present study, the investigators claim that "accumulation of ribavirin by erythrocytes induced no change in their osmotic fragility, indicating that circulating erythrocytes were not made more susceptible to lysis by ribavirin."

Thrombocytosis occurred at [illegible] mg/kg after the treatment period and at 100mg/kg was accompanied by an increase in platelet size. Thrombocytosis was dose-related and appeared to be due, at least in part, to the megakaryocyte hyperplasia in the bone marrow on day 10. Tests of platelet function in vivo & in vitro indicated that there were no treatment-related effects on the platelets. Circulating red cell mass continued to dec after the treatment period until day 16. However, erythroid hyperplasia in the bone marrow and reticulocytosis were present by day 22; recovery from anemia was complete by day 42.

. Dogs treated with ribavirin for 28 days by oral gavage at doses of 15, 30 & 60mg/kg/day showed the following drug-induced toxicities: mortality/moribundity at 60mg/kg; soft stools, mucoid stools and/or diarrhea at 15, 30 & 60mg/kg; sanguinous and/or tarry stools at 30 & 60mg/kg; emesis at 15, 30 & 60mg/kg; ulcerated gums, inappetence/anorexia, progressive physical deterioration, cachexia & marked body wt loss at 30 & 60mg/kg; dec food intake in 15mg/kg F, dec locomotor activity, slow movement/lethargy, depressed, weak, listless and/or ataxic condition, dehydration, tremors, hunched appearance, coat staining (urine), crusty nose & back sores at 60mg/kg.

Hematology data showed evidence of hematological abnormalities consisting of BR decreases in Hct, Hb, RBC count, mean corpusc. volume & mean corpusc. Hb, together with dec reticulocyte counts. These changes were viewed as evidence of "nonregenerative anemia (i.e., a decrease in RBC mass and an absence of reticulocytosis) at 30 & 60mg/kg." Leukocyte cts, lymphocyte #'s and PT's were also dec at 30 & 60mg/kg.

Clinical chem. changes seen at 30 & 60mg/kg consisted of dec in total protein, albumin & globulin (also seen at [illegible] mg/kg). At 60mg/kg there were decreases in sodium, chloride & creatinine phosphokinase and increases in total bilirubin, BUN, alkaline phos., SGOT, glucose, total cholesterol, triglycerides & haptoglobin. Increase in alpha-2-globulin was seen at 30 & 60mg/kg. Urinalysis showed the presence of occult blood and yellow-gold pigment in the urine of 30 & 60mg/kg dogs.

Histopathological evaluation revealed primary involvement of the GI tract, thymus & bone marrow. Principal findings consisted of the following: enteritis characterized by inflammatory infiltrate necrosis

and regeneration of crypt epithelium (15, 30 & 60mg/kg), inc cytoplasmic vacuolation in the stomach (30 & 60mg/kg), severe lymphoid depletion in the thymus (30 & 60mg/kg), and bone marrow hypoplasia (30 & 60mg/kg). Secondary involvement of additional organs consisted of the following: spleen (mod.-severe inc conc'n of brown granular pigment at 30 & 60mg/kg, lymphoid depletion plus lymphoid necrosis at 60mg/kg); liver (brown granular pigment in kupffer cells at 15, 30 & 60mg/kg); adrenals (degranulation of zona fasciculata cells at 60mg/kg) and tonsils (mod. lymphoid depletion at 60mg/kg). Severe to mod. lymphoid depletion was also seen in the prescapular lymph nodes (60mg/kg). Gingival ulceration and ulceration of the scrotum & skin of the chest & leg also occurred at 30 & 60mg/kg. Pancreatic findings (i.e., focal suppurative & chronic pancreatitis and focal & fat necrosis) at 60mg/kg were considered associated with severe drug-induced enteric lesions.

Oral admin. of ribavirin to rats at 30, 60 & 120mg/kg/day for 30 days showed the following: Decreases: body wt & food intake at 60 & 120mg/kg; circulating red cell mass (Hct, Hb & erythocyte ct); haptoglobin (all dose levels); Increases: platelet ct, BUN, glucose & SGOT at all dose levels; SGPT at 120mg/kg; small thymus with lymphoid depletion at 120mg/kg.

USAMRIID: Squirrel monkeys exposed to 40mg/kg/day of ribavirin aerosol for 22 hrs/day continuous exposure for 4 days showed the following: inc in RR on Days 1, 9 & 25 vs. control occurrence of inc on days 1 & 9 only; moderate anemia in C & DT animals with DT being more affected than C (anemia still present on day 25, but hematology values approaching PT values); dec in WBC on days 1 & 5 which was still dec but approaching PT levels on day 25; moderate inc in beta glucuronidase (indicating liver toxicity) on days 1 & 9. The following path. lesions occurred: (1) liver - subacute centrilobular fatty metamorphosis; subacute, suppurative, multifocal hepatitis; mild to diffuse karyomegaly; acute diffuse congestion; (2) kidney - slight to mod. fatty metamorphosis of the tubular epithelium; mod. fatty metamorphosis of the distal convoluted tubules & mod., acute, cloudy swelling of convoluted tubules; (3) pancreatitis; (4) myocarditis.

Squirrel monkeys exposed to IM injections of ribavirin (40mg/kg/day) for 5 days showed anemia in both C & DT, worse in the DT than in C, and elevated BUN indicative of possible renal impairment. No gross or histopath. was performed.

Oral admin. of 40mg/kg/day of ribavirin to monkeys for 5 days produced elevations in SDDT, SGPT & LDH, indicative of possible liver impairment & an inc in BUN.

Monkeys treated for 5 days with 40mg/kg/day of aerosol ribavirin for 5 hrs/day (2.5 hrs in the morning & 2.5 hrs in the afternoon) showed: inc in RR during exposure; dec in physical activity; dyspnea; nasal discharge & white crusting formed around the nostrils; sneezing during exposure. No actual data were submitted for clinical chemistry. Gross & histopath. was not performed.

Admin. of doses of 40 & 400mg/kg/day of ribavirin orally in distilled water to monkeys for 4 days produced the following: dec food intake, dyspnea & dec physical activity at both doses; dec in RBC, Hct, Hb & WBC and inc in LDH at 400mg/kg. No actual data were submitted for clinical chemistry. Gross & histopath. was not performed.

Admin. of ribavirin to rats in a 28-day inhalation toxicity study using whole body exposure chambers and inhaled doses of 22, 36 & 57mg/kg 12 hrs/day for 28 days produced the following: mortality at all dose levels, sig depression in body wt gain at 22 & 36mg/kg (22mg/kg gp died before weekly wts could be obtained), dehydration at 36 & 57mg/kg (i.e., sig elevation in erythrocyte cts, Hct & Hb) at interim sacrifice, sig dec in reticulocyte cts at 36 & 57mg/kg, & sig in Hb, Hct & erythrocytes in ♀ at 36mg/kg at final sacrifice, sig elevations in serum sodium levels in ♀ at 36 & 57mg/kg at interim sacrifice, sig inc in CPK in ♀ at 36 & 57mg/kg, in LDH in ♀ at 36 & in SGOT in ♀ at 57mg/kg. Additional findings consisted of liver wt depression in interim sacrifice ♀ & ♂ at 36 & 57mg/kg and in the 22mg/kg ♀ at final sacrifice. Lung wt elevation occurred in ♂ & ♀ at 36 & 57mg/kg at interim sacrifice and at 22 & 36mg/kg at final sacrifice. Gross lesions consisting of red/gray/brown lung discoloration were observed in ♀ & ♂ at all DT levels. Microscopic lung lesions seen in DT rats (all dose levels) consisted of the following: "alveolar edema & hemorrhage as well as hypertrophy & hyperplasia of intrinsic alveolar epithelial cells (adenomatosis). Lesions were consistent with increased pulmonary vascular permeability & associated multifocal inflammation, and proliferation of the alveolar epithelium." An inc incidence of foam cell (pulmonary macrophages) accumulation in the alveoli was also observed in all DT gps. The following DR lesions were observed in the hearts of the 36 & 57mg/kg dose gps: inflammation of the pericardium & epicardium, frequently associated with myofiber necrosis and interstitial edema. Thymus atrophy characterized by necrosis & loss of cortical cells was observed at 36 & 57mg/kg. Macrophage infiltration of the liver (focal or multifocal) was observed at all dose levels.

Admin. of ribavirin to mice in a 28-day inhalation toxicity study using whole body exposure chambers and inhaled doses of 30, 62 & 111mg/kg 12 hrs/day for 28 days produced the following: mortality at all doses, sig dec in body wt gain at 62 & 111mg/kg, anemia in all DT gps, inc SGOT (SS), LDH & SGPT levels and dec total protein at 111mg/kg, inc in LDH & SGOT (SS) as well as CPK at 62mg/kg The following DR microscopic lesions were observed: "thymus atrophy characterized by necrosis & a reduction of cortical tissues at 111mg/kg, hypocellular sternal bone marrow at 111mg/kg, enteropathy of the large & small intestine at 111mg/kg, necrosis of skeletal muscles of the head (occurred as multifocal coagulative necrosis of the muscle fibers, edema & macrophage infiltration") at 111mg/kg, multifocal mineralization of the heart at all DT levels.

3. Chronic Toxicity Studies:

. Virazole admin. to rats at oral (dietary) doses of 30, 60 & 120mg/kg/day in a 2-year chronic toxicity study, produced a dec in food intake and body wt at all dose levels. A high incidence of drug-induced deaths, alopecia & ulceration of skin, bilateral chronic focal nephritis, chronic focal [illegible]nephritis, an inc in mast cells of the bone marrow of the femoral bone & [illegible]pathological findings concomitant with anemic retinopathy were found at 120mg/kg. Hematological changes indicative of "macrocytic normochromic hemolytic anemia" were also observed at 120mg/kg. Normocytic normochromic anemia was seen at 60 & 30mg/kg.

Virazole admin. to monkeys at oral doses of 30, 60 & 120mg/kg/day for 7 days/week for 6 months resulted in a dec in total leucocyte cts in 1/3 animals (at 3 & 6 mos) at all dose levels. In addition, a dec in erythrocyte cts & Hb was also seen in animals treated at 120mg/kg/day. SAP was dec at all dose levels and 50% of the animals treated at 120mg/kg had mod. to large amts of occult blood in the urine. With respect to histopathology, 17% of Virazole-treated animals (at all doses) presented with portal lymphoid infiltration of the liver. One M at 120mg/kg had chronic focal [illegible]nephritis. One F had focal interstitial lymphoid infiltration of the heart. Differential bone marrow cell cts showed a mod. inc in the myeloid/erythroid ratio at all dose levels.

Admin. of Virazole [illegible]/day at levels providing doses of 15, 30 & 70mg/kg/day in [illegible], 30 & 90mg/kg in F for 15 mos. resulted in a high incidence of deaths (preceded by deep abdominal breathing) and an accumulation of fluid in the subcutis, body cavities & various organs (found dead or to sacrifice) at the 70mg/kg/day dose level. [illegible] wt gain & food intake, hematological indices [illegible] depression in bone marrow production, alopecia, skin [illegible] atrophy of the thymus, spleen & lymph nodes, a dec in [illegible] size of both testes and acute & chronic nephritis was found at all dose levels.

4. Reproductive & Teratology Studies:

Maternal exposure to Virazole (rats) at doses of 30, 60 & 90mg/kg, during the period of fetal organogenesis, resulted in terata among fetuses of all dose gps. The types of malformations observed included exencephaly, anophthalmia, cleft lip, talipes, domed skull, anophthalmia and microphthalmia. Exposure of F to Virazole at doses of 60 or 90mg/kg resulted in embryotoxicity, as evidenced by inc fetal deaths & resorption sites.

Admin. of Virazole at test doses of 30, 60 & 90mg/kg to gravid rats from gestation day 15 through parturition and weaning, resulted in a sig dec in maternal body wt, on day 12 post-partum at the 90mg/kg dose level and a reduction in 12 & 21-day survival indices among pups obtained from dams given 30 & [illegible]mg/kg of Virazole. Virazole-treated dams (90mg/kg/day) fostering pups untreated in utero & control dams

fostering pups exposed to Virazole (90mg/kg/day) in utero showed a dec in the no. of viable pups on lactation days 4, 12 & 21. The dec was greatest among pups weaned by control dams fostering pups exposed to Virazole in utero than by treated dams fostering pups untreated in utero.

. Rabbits treated with Virazole at doses of 0.1, 0.3 & 1mg/kg/day (via gelatin capsules) from gestation day 6 through 18, showed the following: a dec in maternal body wt at 0.1 & 1mg/kg/day; an inc in the number of early & late resorption sites; embryolethality at the 1mg/kg/day level; teratogenicity was not revealed at any dose levels.

. Admin. of Virazole to rats at oral doses of 0.1 & 1mg/kg/day, from day 6-15 of gestation resulted in no adverse effects on treated dams or their fetuses. Admin. of 10mg/kg/day resulted in a dec in body wt in exposed dams, an inc incidence of fetal mortality, reduced fetal body wt, teratogenicity (scoliosis, dome shaped skull, adactylia, macrodactylia, gastroschisis, ureterous & talipes) and an inc incidence of fetuses with retarded skeletal calcification.

. Baboons dosed orally (via banana) with 120mg/kg/day of Virazole for 4 day periods during gestation (day 20-23, 21-27, 28-31, 32-35 & 36-39) showed neither embryolethal nor teratogenic effects. Distension of the gall bladder was seen in the fetuses of mothers treated at 60 & 120mg/kg/day. Adhesions between the ileum & kidney capsule and between the spleen, kidney capsule, ileum & peritoneum was seen in fetuses of mothers treated at 120mg/kg/day.

Ribavirin and 6 of its congeners were evaluated for teratogenic potential in rats. Oral doses of 30 & 90mg/kg/day (day 6 thru 12 of gest.) and 10 & 20mg/kg/day (day 6 thru 15 of gest.) were used. 60mg/kg & above resulted in a sig. embryocidal effect. Surviving embryos of all treatment gps weighed less than controls. Inc intrauterine death was observed following treatment with ribavirin (20mg/kg/day) and all its congeners except 2. Sig reduced fetal wts occurred in all treated gps. Malformed fetuses were seen in all gps except those treated with 2 of the congeners. Malformations were observed in fetuses from 2 gps treated with 20mg/kg/day of ribavirin, but not at 10mg/kg/day. Those seen consisted of gastroschisis, facial abnormalities (cleft lip, cleft palate, anophthalmia) exencephaly and limb & tail defects.

Rats treated by gavage with ribavirin at 20mg/kg/day (during days 6-9, 10-12 & 13-15 of gestation) showed a high incidence of malformations accompanied by a slight inc in embryolethality, when admin. from day 6-9, embryolethality when admin. from day 10-12 of gest. & gastroschisis when admin. from day 13 thru 15. Studies appeared to show that during organogenesis the rat fetus is most sensitive to the teratogenic effect of ribavirin from day 6-9. Treatment subsequent to this period resulted in total embryolethality, and during the later part of gest. produced slight effects on intrauterine development.

Science, January 1977, L. Kilham & V. Ferm: Virazole given in single IP doses on gest. day 8 to pregnant hamsters at doses of 1.25-4.25mg/kg, induced fetal deaths and congenital anomalies of the limbs & eyes (ranging from microophthalmia to anophthalmia) encephalocele, exencephaly, rib defects & 1 case of occult spina bifida.

Teratology 17(2): 249-251, 1978, Kochhar, D.M., J.D. Penner & T.F. Knudsen: Ribavirin, dissolved in saline, when admin. to pregnant mice in single IP doses of 10, 50, 100, 150 or 200mg/kg on gest. days 10-12 produced the following: 100% resorption at a dose of 200mg/kg and resorption & teratogenicity at 50-150mg/kg. Only skeletal malformations were recorded. A high frequency of vertebral, rib, skull, palate, jaw, limb & tail malformations was obtained. All doses reduced embryonic DNA synthesis; 50mg/kg reduced it to 52% & 100 or 200mg/kg to about 25% of the control level. There was also a slight inhibition (80% of control) with the 10mg/kg nonteratogenic dose."

Teratology 17(1): 93-101, 1978, Vergil N. Ferm, Calvin Willhite & Lawrence Kilham: Pregnant hamsters treated with 2.5, 3.75 or 5mg/kg of ribavirin on days 7, 8 or 9 of gest. by single dose IP injection or on day 8 with single dose IV or oral admin. showed the following after IP admin: CNS defects (i.e., encephaloceles & exencephaly), eye defects (microphthalmia, anophthalmia & "open eye"), rib defects including fusions & bifurcations, as well as upper & lower extremity defects (i.e., complete absence of limb to minor abnormalities of the digits), tail abnormalities, prognathism & occult spina bifida at 2.5 & 5mg/kg. After IV admin. of 5mg/kg, the following was observed: resorption rate of 68% with 100% of survivors being malformed; malformations were similar in type to those seen following IP injection. Oral admin. of drug appeared to be more teratogenic than IP admin. Single dose oral admin. of 5mg/kg on day 8 of gest. resulted in only 0.5 embryos (8%) surviving to day 14. Both embryos were severely malformed with eye, rib and upper & lower limb abnormalities & both were markedly prognathic. 63% of fetuses from mothers receiving 2.5mg/kg of drug orally were abnormal." Abnormalities were of the same type noted above for the IP & IV routes. Oral admin. of 2.5mg/kg also produced teratogenicity "with 50% of fetuses showing one or more of the above malformations."

Pregnant rats injected IP on day 9 of gest. with ribavirin at doses of 25, 37.5 & 50mg/kg or given a single oral dose of 25 or 37.5mg/kg on gest. day 9 showed the following malformations after IP dosing: brain (exencephaly & encephalocele), lower limb, tail, facial cleft & mandible hypoplasia at 25mg/kg. The same pattern of malformation was seen at 37.5 & 50mg/kg IP as seen at 25mg/kg IP, with the addition of eye malformations (anophthalmia & microphthalmia); the 50mg/kg IP dose also caused an inc in fetal resorption rate. In rats, teratogenicity was also seen at oral ribavirin doses of 25mg/kg (exencephaly & encephalocele, microphthalmia & anophthalmia, tail malformations, facial cleft & mandibular hypoplasia & severe facial malformations). Oral doses of 37.5mg/kg caused an inc in fetal resorption and the same types of malformations seen at 25mg/kg.

5. Mutagenicity Studies: Total mutagenicity studies performed to date on Virazole in various in vitro & in vivo studies showed the drug to be negative in the dominant lethal assay, the host-mediated assay, cytogenic mutation studies, Ames agar incorporated and suspension assay, Rosenkrantz polymerase assay and positive in the mouse lymphoma mutagenicity assay.

   The Drosophila sex-linked recessive test showed a drug-induced killing of germ cells at or near the time of meiosis (spermatocytes). This effect was attributed to the cytotoxic effect of Virazole.

6. Cell Transformation Studies: Ribavirin induced a big inc in transformed foci in "Sugiura" in the Balb/3T3 in vitro transformation assay, indicating that it is active in this test system.

7. Immunological studies performed using Virazole showed that it was not an immunosuppressant agent in terms of humoral immunity in man, rats, mice & rabbits. However, it did show immunosuppressant activity in terms of humoral immunity in guinea pigs & ferrets when used at doses of 100mg/kg/day or greater. Cellular immunity models indicated that Virazole had a mild immunosuppressant effect at conc'n of 50mg/kg/day and above.

8. Thyroid function studies performed using rats treated with Virazole at doses up to 150mg/kg/day for 11 days showed no morphological alteration in the thyroid or pituitary glands. However, a sig dec in protein bound iodine was found in both M & F treated at 150mg/kg/day.

9. Absorption, distribution & excretion studies performed in rats, monkeys & dogs using radiolabeled Virazole showed urinary excretion as the major route of elimination. Organ storage of ¹⁴C Virazole was minimal. The drug is metabolized by phosphorylation, deribosylation & deamination.

10. Long-term carcinogenicity studies (3) have been performed on Virazole: (1) initiated by Leberle (rat) & Finnegan (mouse) (review of dated 3/17/78), (2) performed in the rat (review of dated 6/10/77), and (3) performed by the using Scrapie infected mice review dated 6/10/78).

    As a result of evaluation of the study data and the carcinogenicity data, there appeared to be an inc incidence in at least 4 types of tumors in Virazole-treated animals. These were pancreatic islet cell adenomas, chromophobe pituitary adenomas, mammary fibroadenomas & pheochromocytomas. The study performed in Scrapie infected mice was reported to be negative.

Conclusion

A. The applicant is proposing use of ribavirin aerosol in the treatment of respiratory syncytial virus (RSV) infection in infants. Drug is proposed for admin.

using the small particle aerosol generator (SPAG). According to the applicant, particle size, recommended dose conc'n (as the stated sol'n in the drug reservoir of the SAG unit) and average aerosol conc'n for a 12-hr period would be 1.2-1.1 micron particle size, 2mg/ml ribavirin & 190mcg/L (0.19mg/L) of air, respectively. The applicant states that "the pulmonary retention fraction has been demonstrated to be 0.75 and that a normal adult will retain 70% of the aerosolized ribavirin, providing a retained dose of 50-55mg/hr of exposure. The applicant is proposing (for the usual dose) continuous exposure for 12-18 hrs/day for 3-5 days.

B. Viratek was informed via FDA letter (see our letter to Viratek dated 5/21/82) as to the types of preclinical inhalation toxicity studies needed to supplement their IND & NDA for the aerosol formulation of Virazole. These studies consisted of acute, subacute (30-day) & subchronic (90-day) inhalation toxicity studies. It was recommended that ribavirin be tested preclinically in the proposed clinical formulation (aerosol sol'n) and in the manner in which it would be used for clinical use (i.e., via small particle aerosol generator, 12 hrs/day using the same particle size proposed for clinical use).

C. Viratek has submitted what they refer to as "inhalation studies" in their NDA [redacted]. These studies are inappropriate in that they involve admin. of the drug in a [redacted]% susp. via the intranasal route, using a plexiglas dispenser or [redacted]. Maximum frequency of drug admin. was 24 sprays q.i.d. x30 days at approx. 3.6mg/spray. These studies do not involve use of the proposed clinical formulation (aerosol sol'n) admin. in the manner in which it will be employed in humans.

D. "No effect" dose levels for inhalation toxicity were not established in the following inhalation studies submitted by Viratek: squirrel monkey study in which animals were exposed to ribavirin at 60mg/kg/day for 20 hrs/day for 4 days via whole body exposure chambers and Toxigenics studies in which rats & mice were exposed for [redacted] day for 30 days via whole body exposure at doses of 30, 60 & 87mg/kg in rats and 30, 62 & 111mg/kg in mice (refer to appropriate studies under Summary & Evaluation of this review for details).

E. According to the applicant, "a normal adult will retain 70% of aerosolized ribavirin, providing a retained dose of 50-55mg/hr of exposure." This would be equiv. to a dose of 600-990mg for a 12-18 hr period. Calculated on the basis of a 50kg man, the highest total daily dose would be 19.8mg/kg/day and the lowest dose would be 10.2mg/kg/day.

F. Generally, the dose recommended for use clinically is a fraction of the "no effect" dose level found in the most sensitive species. Being that "no effect" levels for inhalation toxicity have not been established in preclinical studies submitted by Viratek, a recommendation of an appropriate dose for clinical use cannot be based on available preclinical studies.

G. The 90-day subchronic inhalation toxicity studies recommended to support Phase III clinical trials and/or an NDA, as well as the studies requested

to determine drug effect on lung development in young animals, have never been filed. These studies are still needed and were recommended to the applicant in our letter of 9/7/83.

Despite the applicant's contention that proposed clinical use will entail a single course of therapy lasting 3-5 days, the MO has informed me of the following: that Viratek has reported instances in their NDA in which patients were dosed for as long as 31 days, and that children can be expected to have RSV reinfections until grade school age. Consequently, ribavirin therapy will not be limited to a single dose, but may involve repeated courses of treatment over a number of years. Considering the fact that patients may be treated on a chronic intermittant basis, inhalation toxicity studies (i.e., 90 - 180 days) establishing "no effect" dose levels are still needed. These studies should be accompanied by innalation deposition, retention, clearance & plasma level data.

II. In addition to the absence of sufficient preclinical inhalation toxicity data to determine safety of use, the MO's review of this application dated 11/14/83, concludes that the submission "still remains incomplete, regarding the requirement for substantial evidence on the safety & efficacy of aerosol ribavirin in the treatment of respiratory tract syncytial virus infections in children etc."

I. Ribavirin tested positive in the Balb/3T3 in vitro transformation assay submitted to the IND. However, chemically transformed cells were neither grown in soft agar nor transplanted into syngeneic hosts to establish malignancy and capability of forming tumors, as is required for the in vivo part of this assay. In addition, it is not clear if a metabolic activation system was used. Our letter of Dec., 1976 to recommended both in vitro neoplastic transformation studies and in vivo tumor induction studies. This recommendation is also made in subsequent discussions held with ICN in 1977 and 1978 in D.C. Viratek should be again requested to perform in vitro cell transformation studies (with & without metabolic activation) testing transformed cells for their ability to grow in soft agar & for their in vivo transplantability in susceptible animals.

With regard to the carcinogenicity studies , we now have a statistical review from HFN-210 (Nina Mantel, 11/14/83) which concludes that Viratek's claim of lack of carcinogenicity is not adequately supported by the available data.

Recommendation: Nonapproval

Norma J. Browder, Ph.D.

cc: Orig. IND
HFN-815
HFN-815/MO
CSO
HFN-220
HFN-815/NJBrowder/smc/4/23/84
R/d init.by:JMDavitt
2005a

815 file

# REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 18-859 (Amendment dated 6/18/85)

Date Review Completed: 6/24/85

Applicant: Viratek

Drug: Virazole (ribavirin) Aerosol

Comments:

A. Labeling for ribavirin aerosol has been submitted in this amendment.

B. After discussion and concurrence with the medical officer on 6/21/85, it was decided that the following revisions should be made in the labeling before approval:

1. Under "Warnings" and in the boxed warnings sections, the following statement should be added: "In rats, mice and monkeys, ribavirin administration resulted in cardiac lesions. The significance of these findings to human administration is unknown."

2. In the "Adverse Reactions" section, the second sentence in the first paragraph should be changed to read: "In infants, ribavirin aerosol use has rarely been associated with worsening of signs of respiratory tract disease, pneumothorax and rash. Reticulocytosis has been observed in infants, but the frequency is not known. Monkeys administered 30mg/kg/day or more of ribavirin for 10 days showed a reduction of red blood cell counts, hematocrit and hemoglobin during treatment; reticulocytosis was observed 12 days after treatment was stopped."

3. MORS's (#5, 10 & 11) refer to adverse reactions or events "which are associated with ribavirin use and cannot be attributed to other causes with certainty," and are therefore possibly related to ribavirin. It is recommended that a summary of these findings be incorporated into the "Adverse Reactions" section.

4. The "Adverse Reactions" section currently states: "Anemia, which occurs frequently with oral and intravenous ribavirin, has not been shown to be associated with use of the aerosol." It is noted that the MOR for the oral formulation ( reports several clinical instances in which anemia was not detected until a number of days after initiation of treatment. The reported absence of anemia in association with use of the aerosol may be due to the fact that the duration of follow-up in patients receiving the aerosol was inadequate to detect anemia. It would probably be more accurate if this section of the labeling were revised to read as follows: "Anemia, which occurs frequently with oral and intravenous ribavirin has not been adequately studied during the appropriate follow-up periods in patients receiving the aerosol."

C. This amendment also contains studies for two oral feeding carcinogenicity protocols. After review of these protocols, the following recommendations are made: Agency policy calls for carcinogenicity studies in two species. It is not clear whether Viratek plans to do these studies in two species, or a single study in one species. It is recommended that the studies employ two species. One of these studies should be performed by the oral route (via gavage), with some animals allocated for plasma level determinations. The other should be done using inhalation or intratracheal instillation.

D. The following additional preclinical studies have been recommended for performance post-marketing:

1. "Study of physical-chemical and pharmacologic interactions of ribavirin with digoxin, aminophylline, other bronchodilators and antibiotics." (See MOR (#12) dated 4/25/85.)

2. Study of drug-induced toxicity in neonatal animals. These studies were requested in our letter to Viratek dated 9/3/83.

3. Study of drug disposition, retention & clearance as well as systemic exposure (blood & urine levels) following inhalation. These studies were requested in the pharmacology review of the aerosol NDA dated 3/26/84, (in a memo of telcon with Viratek dated 12/19/83 and in our 9/3/83 letter to Viratek, re:

Norma J. Browder

Norma J. Browder, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/NJBrowder/smc/7/26/85
R/d init.by:JMDavitt
0015p

STAT REV

# Statistical Review and Evaluation

Date: AUG 23 1985

NDA #: 18-859/Drug Class: 1A

Applicant: Viratek

Name of Drug: Virazole (ribavirin) Aerosol

Documents Reviewed: Amendment 56 dated April 15, 1985

This review pertains to a clinical study evaluating the safety and efficacy of Virazole for the treatment of hospitalized infants with respiratory syncytial virus (RSV) infections. Previous studies submitted to this NDA have undergone statistical reviews dated November 15, 1984 and March 4, 1985. Clinical input has been provided by V. Schauf, M.D., HFN-815.

## Barry-Cockburn Study

This two center, randomized, placebo-controlled study was conducted during two winters (1982-1984) in the United Kingdom. A restricted randomization scheme was used to balance infants in Ribavirin and placebo groups for important progostic factors: age, arterialized capilliary pCO2, respiratory rate and interval since onset of cough or breathlessness.

Before trial entry, and at three times daily until recovery, infants were examined and the following data were recorded:

Apnoeic episodes, cyanotic episodes and/or cough-each rated as none, occasional or frequent;

Nasal discharge - rated as none, slight or profuse;

Feeding behavior - rated as normal, slow, tube-feeding or parenteral feeding;

Attitude - rated as alert, drowsy or distressed;

Nasal flaring, wheeze, chest recessions - each rated as none, mild or marked;

Rhonchi and crepitations - each rated as none, localized or widespread;

Respiratory rate and heart rate per minute;

Requirement for oxygen enrichment of inspired gas;

Overall impression - rated on a 100 mm visual analogue scale, from completely well (0 mm) to moribund (100 mm);

Transcutaneous partial pressure of oxygen (pCO2) was measured in all infants daily.

The treatment groups appeared to be comparable in prognostic factors and baseline measures. In checking for comparability, this reviewer found that average values reported by the sponsor for age, weight, capilliary pCO2 and onset interval were incorrect.

The following items of data were analyzed using the time interval between starting treatment and first sustained observation of a) improvement and b) normalization - Apnoeic episodes, cyanotic episodes, cough, nasal discharge, feeding behavior, attitutde, nasal flaring, wheeze, chest recession, rhonchi and crepitations.

Any patient whose score was at the lowest level for a factor (e.g., none or normal at baseline) was excluded from the analyses of time to improvement and time to normalization for that factor. Treatments were compared using Wilcoxon's rank sum test.

Data on respiratory rate, heart rate, overall impression, and transcutaneous pCO2 obtained before treatment started and in the first 120 hours after treatment started, were analyzed using a slope-analysis. That is, least-squares slopes were fit to each patient's observations (regressed on time from start of treatment). T-tests were then used to compare treatment groups with respect to normalized values of the slope estimates. Heart rate data were converted to logarithms and overall impressions data to angles prior to analysis, in order to produce approximately straight regression lines.

Table 6, provided by the invectigators (with some correction by this reviewer), provides analyses of time to improvement and time to normalization for the 11 indices for (1) all patients, (2) patients with virological confirmation of RSV, and (3) patients with virological confirmation who did not take concomitant antibiotic treatment. Of these, Dr. Schauf advises me that the most appropriate subgroup for this NDA consists of patients with virological confirmation of RSV. Only this subgroup will be discussed in this review. This reviewer checked the results of all reported significant results for patients with virological confirmation of RSV. The results for nasal flaring were incorrect and the difference between drugs was not significant ($Z=1.16$, $p=0.24$) for both time to improvement and time to normalization. A few median values were incorrect also. (Note that this reviewer found that a number of rank sum values for the analyses of the 'all patient' data presented in the submission were illogical; therefore the p-values for 'all patients' in Table 6 are not reliable.)

For infants with confirmed RSV, significant differences between groups favoring ribavirin were seen in time to normalization for feeding behavior and attitude, and in time to improvement for chest recession and crepitations.

The estimated regression slopes for overall impression, heart rate and respiratory rate over time were negative for all infants, thus indicating improvement for each one. The transcutaneous pCO2 (TCPO2) values for 9 out of 11 infants on active drug and 7 out of 9 infants on placebo indicate that most infants improved for this measure also. Table 2, also supplied by the sponsor, provides the results of the comparisons of the Normalized (using normal scores) differences between linear regression coefficients for the two treatment groups among all infants, those confirmed to have RSV by virology, and those confirmed RSV cases who did not take concomitant antibiotics. Although the sponsor did not state what the values were in table 2, they appear to be mean differences of the normalized scores + the standard error of the difference. These tests did not indicate a significant treatment difference for any of the three subgroups; those infants with confirmed RSV showed negligable differences in rates of improvement for heart rate, respiratory rate and TCPO2.

There was no significant difference between the two treatment groups in the mean duration of treatment (67.8 hours for ribavirin, 65 hours for placebo) or in the days of viral shedding (median 3.5 days for ribavirin, 4 days for placebo). Viral infectivity was measured either by immunofluorescence and/or cell cultures of nasal washes.

Overall conclusion

Although all patients in this study improved and the mean duration of treatment for the ribavirin and placebo groups were comparable, ribavirin appeared to speed up the recovery of some symptoms of RSV (time to improvement of chest recession and crepitations, and time to normalization of feeding behavior and attitude). The importance of these results must be interpreted on clinical grounds. Although the submission reported that treatment differences in time to improvement and time to normalization of nasal flaring were significant, reanalysis indicated that the results were not significant ($p=.24$ for both analyses).

Many unexplainable errors were found in this submission. incorrect averages, illogical rank sum values, incorrect medians, incorrect p-values from the analysis of nasal flaring. The results reported based on re-analyses in this review assume that the raw data listings in the submission are correct. Such an assumption might be questioned considering the poor quality of the

investigators' data analyses. The results from this study should therefore not be accepted without case report forms to check the accuracy of extracted data.

James R. Gebert

James R. Gebert, Ph.D.
Mathematical Statistician

cc:
Orig. NDA 18-859
HFN-815
HFN-815/Dr. Schauf
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Gebert
Chron.
File: DRU 1.3.2 NDA
JGebert/rp/8/20/85 #1500r

Concur: Dr. Johnson MJ 8/21/85

Dr. Dubey MJ for SDD 8/21/85

TABLE 6

SUMMARY OF DATA ON TIME INTERVALS TO IMPROVEMENT AND NORMALISATION OF CLINICAL SIGNS OF BRONCHIOLITIS

| Index | I/N | All patients | | | | | Patients with virological confirmation | | | | | Patients with virol. confirmn. and no antibiotic treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Active | | Placebo | | p[3] | Active | | Placebo | | p[3] | Active | | Placebo | | p[3] |
| | | n | Median | n | Median | | n | Median | n | Median | | n | Median | n | Median | |
| Apnoeic episodes | I | 4 | 17.5 | 5 | 24.5 | NS | 3 | 16 | 5 | 25 | NS | 3 | 16 | 4 | 36.7 | NS |
| | N | 4 | 17.5 | 5 | 24.5 | NS | 3 | 16 | 5 | 25 | NS | 3 | 16 | 4 | 36.7 | NS |
| Cyanotic episodes | I | 7 | 16 | 2 | 19.25 | NS | 4 | 16 | 2 | 19.25 | NS | 4 | 16 | 1 | 19 | NS |
| | N | 7 | 16 | 2 | 19.25 | NS | 4 | 16 | 2 | 19.25 | NS | 4 | 16 | 2 | 19 | NS |
| Cough | I | 14 | 25.5 | 12 | 66.5 | L.05 | 10 | 25.5 | 9 | 66.5 | NS | 9 | 25.5 | 6 | 66.5 | L.05 |
| | N | 14 | M90 | 12 | M90 | NS | 10 | 70 | 9 | 103 | NS | 9 | 69.5 | 6 | M74 | NS |
| Nasal discharge | I | 10 | 28.5 | 10 | 40.2 | NS | 6 | 43.5 | 7 | 23.5 | NS | 5 | 43.5 | 4 | 19 | NS |
| | N | 8 | 22.25 | 8 | 31.5 | NS | 6 | 43.5 | 7 | 32 | NS | 5 | 43.5 | 4 | 31.5 | NS |
| Feeding behaviour | I | 14 | 21 | 12 | 43 | NS | 10 | 25 | 9 | 49 | NS | 9 | 21 | 6 | 49 | NS |
| | N | 14 | 43.25 | 12 | 62 | L.05 | 10 | 27.75 | 9 | 69 | L.05 | 9 | 22.5 | 6 | 49 | NS |
| Oxygen requirement | N | 4 | 37.3 | 3 | 25 | NS | 4 | 37.3 | 3 | 25 | NS | 3 | 25.5 | 1 | 56 | NS |
| Attitude | I | 10 | 19 | 6 | 43 | NS | 5 | 18 | 6 | 36.7 | NS | 5 | 18 | 5 | 43 | L.05 |
| | N | 12 | 22.8 | 6 | 43 | NS | 8 | 21 | 6 | ~~33.5~~ 43 | L.05 | 7 | 19 | 5 | 43 | L.05 |
| Nasal flaring | I | 9 | 19.25 | 10 | 26.25 | NS | 7 | 19 | 9 | 28 | ~~L.05~~ NS | 7 | 19 | 6 | 45.5 | L.05 |
| | N | 9 | 19.25 | 10 | 26.25 | NS | 7 | 19 | 9 | 28 | ~~L.05~~ NS | 7 | 19 | 6 | 45.5 | L.05 |
| Wheeze | I | 13 | 21.2 | 11 | 20.5 | NS | 10 | 22.5 | 9 | 21.4 | NS | 9 | 22 | 6 | 19 | NS |
| | N | 13 | 40 | 11 | 28.5 | NS | 10 | 41.8 | 9 | 23.8 | NS | 9 | 40 | 6 | 33.5 | NS |
| Chest recession | I | 14 | 21.2 | 12 | 36 | NS | 10 | 19.25 | 9 | ~~45.5~~ 40 | L.05 | 9 | 19.5 | 6 | 50 | NS |
| | N | 14 | M69 | 12 | M72 | NS | 10 | M90 | 9 | M72 | NS | 9 | M66 | 6 | M74 | NS |
| Rhonchi | I | 12 | 23 | 9 | 24 | NS | 9 | 24.2 | 8 | 23.8 | NS | 9 | 25.5 | 5 | 48 | NS |
| | N | 12 | 51.75 | 9 | 74 | NS | 9 | 48.2 | 8 | 74 | NS | 9 | 48.25 | 5 | 74 | NS |
| Crepitations | I | 13 | 25 | 12 | 48 | L.05 | 9 | 22 | 9 | ~~75.5~~ 75 | L.05 | 8 | 24.5 | 6 | NV | NS |
| | N | 13 | 68 | 12 | NV | NS | 9 | 68 | 9 | M72 | NS | 8 | 68 | 6 | M74 | NS |
| Heart rate[1] | N | 14 | 69.2 | 11 | NV | NS | 10 | 47.5 | 8 | 64.2 | NS | 9 | 46.5 | 5 | 56 | NS |
| Respiratory rate[2] | N | 14 | 49.75 | 12 | 64 | NS | 10 | 49.6 | 9 | 72.5 | NS | 9 | 48 | 5 | 32 | NS |

I = time to improvement (hours); N = time to normalisation (hours); L = less than; M = more than;
1 = normal (less than 110/min); 2 = normal (less than 43/min); 3 = Wilcoxon rank sum test.

Table 2

Treatment Differences (Normal scores)

(Positive differences favour the active group)

| | Overall | Viral cases | No-other-drug cases |
|---|---|---|---|
| Overall impression | 0.54±0.39 | 0.43±0.51 | 0.37±0.43 |
| Heart Rate | 0.33±0.33 | 0.04±0.42 | 0.41±0.34 |
| Resp. Rate | 0.35±0.39 | 0.05±0.40 | 0.42±0.33 |
| TCPO2 | 0.56±0.37 | 0.03±0.46 | 0.85±0.41 |

# BIODIS

# REN

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

DATE : SEP 03 1985

TO : Edward Tabor, M.D.
Director, Division of Anti-infective Drug Products

FROM : Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics

SUBJECT: Biopharmaceutics Recommendation for Deferral
Ribavirin (Virazole) Aerosols NDA #18-859
Viratek Submissions dated: 06/18/85 & 11/04/83

## I. BACKGROUND:

Ribavirin (Viratek's Virazole$^{R}$) is a synthetic, non-interferon inducing, nucleoside analogue of guanosine, existing in two crystalline polymorphs. It is colorless, water-soluble, and has remarkably broad spectrum of selective antiviral effects against a wide range of both DNA and RNA viruses, especially when tested in vitro.

Ribavirin is indicated for the treatment of respiratory syncytial virus (RSV), for which there is currently no known treatment. Hence, ribavirin is claimed to be a life-saving drug indicated for the "treatment of carefully selected hospitalized infants with severe lower respiratory-tract infections due to RSV." It is to be noted that ribavirin aerosols are not to be administered to patients via artificial respirator (i.e., through endotracheal tube) due to drug crystallization occurring in the ventilator. However, ribavirin aerosols delivered by other techniques (viz., hood, mist tent, or face mask) which do not require assisted ventilator are acceptable to the Agency. Long-term aerosol treatment is recommended in the labeling to be carried out for 12-18 hours per day for at least three but no more than seven days.

## II. SUMMARY OF SUBMITTED PHARMACOKINETIC STUDIES

The submission dated November 4, 1983 included eight clinical pharmacokinetic studies, as outlined below.

| Study No. | Route | n | Patients | Study Design |
|---|---|---|---|---|
| 1 | p.o. | 4 | Adults | 1000 mg/day (t.i.d.); 10 days (one sample = 2.5 h) |
| 2 | IV Bolus | ? | Adults | Day #1: 1000 mg (Loading)<br>Days 1-4: 1000 mg (q.i.d.)<br>Days 5-10: 500 mg (t.i.d.)<br>(one sample per dose = 2.5 h) |
| 3 | Inhalation (face mask) | 4 | Pediatric | 2.5 h/day; 3 days (2mg/kg/d) |
| 4 | Inhalation (mask or tube) | 4 | 3 Children | 5.0 h/day; 3 days (4 mg/kg/d) |
| 5 | Inhalation (mask or tube) | 3 | Pediatric | 8.0 h/d; 3 days (6.6 mg/kg/d) |
| 6 | Inhalation (mask or tube) | 3 | Adults | 04 h, bid (Day 1)<br>12 h qD (Day 2)<br>04 h, qD (Day 3) |
| 7 | Inhalation (mask or tube) | 4 | Pediatric | 20 h/d; 5 days (Cmax only) |
| 8 | Inhalation (various) | 2 | Pediatric | Courses 1-2: 5- & 10-d duration<br>" 3-4 = 26 d (3 dose levels) |

## III. CONCLUSION

Data submitted by the firm were insufficient to meaningfully define the pharmacokinetic characteristics of ribavirin aerosols delivered by different inhalation techniques. There was very limited patient information, many diversified experimental variables, and incomplete biostudy data (e.g., missing plasma concentration-time profile data points).

## IV. RECOMMENDATION

The Division of Biopharmaceutics recommends the approval of NDA #18-859 under Section 21 CFR 320.22 (e) of Agency's Bioavailability requirements (i.e., for good cause). Under this CFR Section, the Division does not waive the requirement for in-vivo data but instead defers it. Therefore, the firm should agree in writing to conduct a well-controlled, Phase-IV study(ies) to better define this drug's pharmacokinetic/bioavailability behavior in order to support the labeling's approved dosing regimen.

In the attached review are recommended labeling changes for this product as well as studies' deficiencies that should be communicated to the firm.

Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics

Prepared by: T.E. Mary Ong-Chen
Initialed by: C.T. Vishwanathan, Ph.D. 5/27/85

cc: HFN-220 (Skelly), HFN-226 (Chen), Drug, Review, & Chron Files

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

DATE : SEP 03 1985

TO : Edward Tabor, M.D.
Director, Division of Anti-infective Drug Products

FROM : Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics

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| 7 | Inhalation (mask or tube) | 4 | Pediatric | 20 h/d; 5 days (Cmax only) |
| 8 | Inhalation (varicus) | 2 | Pediatric | Courses 1-2: 5- & 10-d duratio<br>" 3-4 = 26 d (3 dose levels |

## III. CONCLUSION

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In the attached review are recommended labeling changes for this product as well as studies' deficiencies that should be communicated to the firm.

Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics

Prepared by: T.E. Mary Ong-Chen
Initialed by: C.T. Vishwanathan, Ph.D. 5/27/85

cc: HFN-220 (Skelly), HFN-226 (Chen), Drug, Review, & Chron Files

Ribavirin
Virazole[R] Aerosols
(Lyophilized Powder for Reconstitution)
NDA #18-859
Reviewer: T.E. Mary Ong-Chen
Wang #[redacted]

Viratek
(a Nucleic Acid Development Co.)
Cavino, California 91722
Submissions Dated: 06/18/85 &
11/04/83

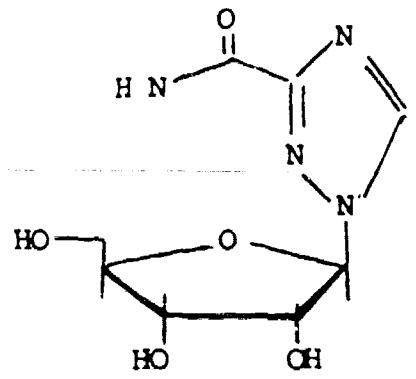
SEP 03 1985

Review of Eight Pharmacokinetic Studies and Labeling

## I. BACKGROUND

Ribavirin is a synthetic, non-interferon inducing, nucleoside analogue of guanosine. It has remarkably broad spectrum of selective antiviral effects against a wide range of both DNA and RNA viruses, especially when tested in vitro. The drug is converted in the liver and other tissues to ribavirin phosphate derivatives (initially activated by cellular enzyme to ribose 5'-monophosphate and subsequently to ribose-5'-diphosphate and triphosphate); thus blocking a critical step in the biosynthesis of guanine nucleotides, which in turn inhibits viral nucleic acid (both RNA and DNA) syntheses in infected cells. Ribavirin is, however, not considered to be virucidal but virustatic; its in-vitro inhibitory effect against viral diseases is found to be reversible when the drug was removed.

Chemically, ribavirin consists of D-ribose attached to 1,2,4-triazole carboxamide. The molecular weight is 244.21 Daltons.




Ribavirin
(1-Beta-D-ribofuranosyl-1,2,4-Triazole-3-Carboxamide)

It is colorless, water-soluble (142 mg/ml), and chemically stable. Two crystalline polymorphs of ribavirin were reported: one form has a melting point at 166-168°C (in aq. ethanol), the other melts at 174-176°C (ethanol). Both exhibit equal biological activity.

Ribavirin has been an experimental antiviral drug for treatment of lower respiratory syncytial virus (RSV) infection. The RSV is identified as the most important respiratory pathogen in infants and young children (in adolescence as well). The virus is associated with 32% to 75% of pneumonias in this age group. According to the medical staff of HFN-815, it is a life-saving drug.

Included in the submission dated November 4, 1983 are a very brief summary the RIA method, a copy of the 'Package Insert', and a paper entitled "Ribavirin Pharmacokinetics in Children and Adults during Therapeutic Trials" consisting of eight clinical studies.

The clinical pharmacokinetic studies were conducted on a variety of patient groups who were given either or different means of aerosol ribavirin therapies for several periods of duration over a broad range of dosages for therapeutic courses of various viral infections. Results and conclusion for the different studies described in this review were the results and conclusions as presented by the sponsor.

For the studies results which are presented in this paper, the assay procedure used is summarized as follows as described by the sponsor. Unlike other nucleoside analogs which are in clinical use or candidate antivirals, ribavirin lacks an ultraviolet absorption spectrum that is useful for spectrophotometric analysis of clinical samples. Therefore, there has been very limited studies of the absorption and disposition of this antiviral compound.

A couple of years ago, a radioimmunoassay (RIA) for ribavirin was developed by Austin, et al. to measure drug levels in plasma after several dosing regimens in humans [ cf., Antimicrob. Agents & Chemother. 24(5):696-701, 1983 ]. The authors claimed that their method was capable of measuring ribavirin levels in a large number of clinical samples with maximum sensitivity and specificity. They employed the standard competitive binding RIA technique using [$^3$H]-ribavirin as antigen and rabbit antiribavirin as antibody. The assay was run at pH 7.6 with 0.4 picomole of [$^3$H]-ribavirin. The antiserum was prepared against mono-succinylated ribavirin conjugated to ovalbumin. The antiserum is highly specific for ribavirin and its triphosphate nucleotide. It has minimal (2-5%) cross-reactivity with the major ribavirin metabolite (triazole carboxamide) and no cross-reactivity with other ribavirin catabolites or other naturally-occurring nucleosides or nucleotides. Clinical samples (plasma, serum, urine, respiratory tract secretions, etc.) can be assayed in the RIA without any special processing. Fig. 1 illustrates a representative standard curve for ribavirin as a log-logit plot of percent relative binding versus concentration of ribavirin (i.e., 0.19-100 picomoles of ribavirin per 100 ul). The sensitivity of the ribavirin RIA was reported at approximately 0.002 ug/ml or 0.01 uM.

With this assay, the sponsor was able to measure the ribavirin concentration present in clinical samples from patients who received aerosol ribavirin therapies. They indicated that these data had allowed some primary assessments of the appropriateness of empirical dosages currently in use to treat patients, to make comparisons of drug levels as a function of dosage and route of administration, and to estimate plasma and secretory half-life values and drug clearance rates from plasma and respiratory tract secretions.

In a meeting on July 25, 1985 with the reviewing medical officer in HFN-815, the following points were discussed regarding this submission and its revised drug labeling submitted to the Agency on June 18, 1985 (see APPENDIX B for details).

1. Ribavirin is a life-saving drug indicated for the "treatment of carefully selected hospitalized infants with severe lower respiratory-tract infections due to respiratory syncytial virus (RSV);"

2. There is currently no known vaccine against RSV except by experimental ribavirin aerosol therapy; however, caution should be made that this drug has been found to be carcinogenic, teratogenic, and/or embryolethal in tested animals;

4. Aerosol treatment is to be carried out in the hospital for 12-18 hrs per day for at least 3 but no more than 7 days (n.b., the standard solution in the drug reservoir of the generator is to be 20 mg/ml);

5. That the paper entitled "Ribavirin Pharmacokinetics in Children and Adults during Therapeutic Trials", which was submitted by the sponsor in their NDA in support of its labeling, is published in Clinical Applications of Ribavirin, edited by R.A. Smith, et al., 1984, Academic Press, Inc.

## II. PHARMACOKINETIC STUDIES

This submission included fragments of pharmacokinetic information from a series of preliminary clinical studies which are reviewed below. Pharmacokinetics of ribavirin were investigated in both children and adult patients following (therapeutic) dosing via [redacted] and aerosol routes of administration. Individual studies are described below. Tables and Figures cited each study are attached in APPENDIX A

C. AEROSOL THERAPY:

Apparatus: Collison Aerosol System (see Fig. 2 for illustration)

The use of aerosol-producing system was pioneered by Collison (in 1975) and further adapted by many investigators, such as U.S. Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland. Fig. 2 illustrates the apparatus used by Knight et al. of Baylor University in 1981 to generate continuously flowing aerosols containing ribavirin for use in respiratory therapy (cf., Lancet 1981:945-949). At a constant flow rate of nebulized aerosol from a reservoir with a moderate volume of drug in solution, it is theoretically possible to deliver increasing amounts of drug into the respiratory tract with a direct relationship to duration of aerosol treatment. The dosage can be increased by increasing the concentration of drug in the reservoir or by increasing duration of the aerosol treatment or both; monitoring of therapy can be accomplished by assessment of drug levels in plasma and in respiratory secretions. The actual aerosol dosage was estimated as given in Table III.

The sponsor applied the concept of treating respiratory infections by the respiratory route of drug administration; therefore, the aerosol use of ribavirin in the treatment of respiratory viral infections has led th way to the development of a new concept of chemotherapy through "compartmental" administration. Since therapeutic trials of ribavirin were initiated in 1980 with small-particle aerosols (SPA), plasma and respiratory tract secretion data have been made available from a variety of patient groups receiving ribavirin aerosol therapy. The pharmacokinetic parameters can now be used to make recommendations about the clinical usage of aerosol ribavirin therapy in hospitalized patients and to further assess the practicality of using this therapy in both an outpatient and office setting.

1. SHORT-TERM AEROSOL THERAPY (see Studies 3 through 5 below)

BETWEEN STUDY COMPARISONS

d) Relationships Between Plasma Concentration and Drug Accumulation and Duration of Therapeutic Treatments (Tables VII-VIII)

The sponsor indicated the plasma ribavirin levels increased with the duration of aerosol treatments; the mean peak ribavirin levels rose from 0.76 uM to 4.4 uM for 2.5 h and at 8 h of duration of therapy, respectively (see also Table VII).

| DOSE | PLASMA Cmax AFTER 3-DAY AEROSOL THERAPY (uM) Grand Mean | Dose 1 | Dose 2 | Dose 3 |
|---|---|---|---|---|
| 2.5 h | 0.76 | 0.6 | 1.1 | 1.0 |
| 5 hour | 1.10 | 1.3 | 1.4 | 1.1 |
| 8 hour | 4.40 | 3.3 | 3.5 | 6.1 |

Mean peak values following dose 1, dose 2, and dose 3 showed no accumulation over a course of therapy until 8-hour treatments were given for 3 days (Table VIII). At this prolonged aerosol treatment, the plasma ribavirin levels rose from a mean of 3.5 uM at Dose # 2 to 6.1 uM at Dose # 3. The rise in plasma ribavirin concentrations perhaps indicates that drug was accumulating between Doses No. 2 and No. 3.

e) Relationship Between Respiratory Secretion and Drug Accumulation and Duration of Therapeutic Treatments (Table X & Fig. 6)

The sponsor indicated that of the three patients who were on assistive ventilation (i.e., via endotracheal tube), respiratory-tract secretions were obtained for analysis (n.b., two were on 5 hours of therapy and one on 8-h therapy). There existed a substantial rise in endotracheal concentrations of ribavirin for the patient who was treated with 8 hours of therapy (Fig. 6). The mean peak levels of ribavirin in endotracheal secretions usually occurred at the end of aerosol therapy and ranged from 1,000-7,700 uM (Table X).

The sponsor claimed that these studies provided substantial documentation that ribavirin may indeed reach the site of infection in the respiratory membrane at a concentration sufficient to inhibit viral replication as the MIC for RSV is 12-40 uM.

f) Relationship Between Half-lives and Drug Accumulation and Duration of Therapeutic Treatments (Tables IX & X)

The average half-life of ribavirin in plasma was estimated at 9.4 h and ranged from 6.5 to 11 h (Table IX). The sponsor stated that its higher value, as compared to that previously reported, may have been due to repository in lung tissue with slow transport across the respiratory membrane into alveolar capillaries (and into the vascular space) and/or back-feed into plasma from repository in old red blood cells, trapped by phosphorylation, released by "aging lysis" of RBC with dephosphorylation in plasma.

The half-life of ribavarin respiratory secretions appeared to be short. The estimated values ranged 1.4 to 2.5 h (Table X). The sponsor addressed the short half-life in secretions as being due to drug transport across the relatively great expansion of the respiratory membrane, clearance by respiratory macrophages and by upward ciliary motion, or all of these.

The half-lives of ribavirin in both plasma and respiratory secretions did not appear to change with duration of therapeutic treatments (cf., Tables IX & X).

2. LONG-TERM THERAPEUTIC TREATMENTS (Studies 6-8)

b) Study 7: (Tables XI & XII; Figs. 8 & 9)

Dr. [redacted] had given immunosuppressed pediatric patients with life-threatening respiratory viral infections a ribavirin aerosol treatment of 20-hours duration for periods of 5 days or more. Various routes of administration (viz., mist tent, face mask, and respirator) were utilized depending upon the patient's age and degree of respiratory distress.

The sponsor, on the other hand, monitored the plasma and respiratory secretion levels of ribavirin from these patients very closely since some of them have received aerosol therapy for prolonged or repetitive courses in an effort to eradicate their persistent or recurrent infections.

For a group of these patients who received 5 days of aerosol therapy, 20-h treatment per day, peak plasma ribavirin levels were recorded (Table XI). The mean peak levels ranged from 2.7 to 13.2 uM with the highest plasma levels being associated with those patients (e.g., Patient # [redacted]) who were intubated.

For patients [redacted] given long-term (20-h) endotracheal route of ribavirin therapy, the mean ribavirin peak concentration in respiratory secretions were observed at approximately 12.3 mM ranging from 1.25-28.2 mM (NOTE: in millimolar range). (Table XII)

The firm gave rationale that the high concentration in respiratory secretion may account for the observed marked rise of the ribavirin concentration in plasma.

| | |
|---|---|
| Study: | Standard ribavirin aerosol therapy in children with respiratory viral infections |
| Sites: | [redacted] |
| Sponsor: | Viratek |
| Subject: | Immunosuppressed patients |
| Age Group: | Infants (2, 5, & 8 mo; 8.5 y) |
| Gender: | Unknown (?) |
| Weight: | Unknown (?) |
| Diseased State: | Life-threatening respiratory viral infections |
| Route: | Various routes: face mask, respirator, mist tent |
| Duration | 20 h/d for 5 days or more (one dropped out at 2 h) |
| Regimen: | Various courses of therapy |
| Specimens: | Plasma & respiratory secretions |

PEAK CONCENTRATION (uM)

| Patient | Age | Route | Plasma Mean | Plasma Range | Resp. Secretion Mean | Resp. Secretion Range |
|---|---|---|---|---|---|---|
| [redacted] | 2 mo | E.Tube | 13.2 | [redacted] | | |
| (1st) | 5 mo | M.Tent | 8.1 | | | |
| (2nd) | 5.5mo | " " | 9.5 | | | |
| * | 8 mo | E.Tube | -- | | | |
| @ | 8.5 y | F.Mask | 2.7 | | | |
| MEAN | | | | | 12,300 | [redacted] |

* Liver Failure
@ 6-d therapy

c) Study 8: (Fig. 9)

The course of aerosol therapy in this study was very similar to that described in Study #7, with the exception that dose administered varied by altering the concentrations of ribavirin solution in the reservoir.

For example, Patient [redacted] had received four courses of aerosol therapy: two of 5-day duration (reservoir concentration of 10 mg/ml) and two of 10-day duration (where the 3rd course of therapy was given with a concentration of 25 mg/ml of ribavirin in the reservoir); this probably cause a rising plasma concentration during that period, as depicted in Fig. 8.

Similarly, Patient [redacted] received a long-term ribavirin therapy by hand nebulized with reservoir concentrations of 10, 20, and 30 mg/ml of ribavirin over the 26 days of treatment. There were corresponding rises in plasma concentration reaching 70 uM peak level at the end of therapy. (Fig. 9)

FIRM'S OVERALL PLAN: The firm pointed out in the November 4, 1983 submission of their desire to perform therapeutic studies of aerosol ribavirin using rising doses; they would aim at elucidating the relationship between dosage, route of administration, tolerance, and toxicity with rising doses.

NOTE: The sponsor indicated in the November 4, 1983 submission that they would be conducting additional studies for and aerosol administration to better define the efficacy, safety, and pharmacokinetics of Virazole. In a meeting with the reviewing medical officer in HFN-815 on July 25, 1985, Dr. Schaub indicated that no new studies had been filed.

## III. OVERALL DEFICIENCIES

1. The firm provided summary results for eight studies that were carried out in different aged patients (infant to adult) using different doses by different routes of administration. Most of those studies were carried out such that the drug was not given as prescribed in labeling's DOSAGE AND ADMINISTRATION Section (i.e., treatment for 12-18 hours per day for at least three and no more than seven days). These studies, as a whole, are deficient in that:
   a) the studies can only be considered as pilot studies due to the small number of patients (i.e., 2-4 subjects) enrolled per study,
   b) no assay validation data were provided per study,
   c) incomplete demographic data were provided,
   d) only minimal tabular data (i.e. plasma profiles) were provided, and
   e) the method of calculating drug's half-life was not described;

2. Some studies' results to support certain statements of the labeling in the 'Pharmacokinetics' Section (e.g., metabolism and excretion) were not provided. The firm should provide information/data to support those labeling statements or retract them from the labeling.

## IV. COMMENTS

1. The firm should modify the drug labeling to incorporate more specific information for each study that is cited (e.g., number of patients, patient's age groups, diseased states, dose administered, and exact modes of drug administration). For example, the label may be stated as:

   - "Following oral dosing of 1000 mg/day given in three divided doses for 10 days in four ADULT patients, plasma ribavirin concentration ranged [redacted] uM after 2.5 hours with a mean concentration of 3.1 uM."

   - "Four PEDIATRIC patients inhaling ribavirin aerosols administered by face mask for 2.5 hr each day for three days had plasma concentration range of [redacted] uM at 2.5-hr postdose with a mean concentration of 0.76 uM." The plasma half-life was reported to be 9.5 hr.

   - ETC. (continued as for other doses).

   - " X pediatric patients were given ribavirin aerosols therapy by (face mask, mist tent, air hood) for Y hr each day for Z days, plasma concentrations range was shown between U uM and V uM after W hr with mean concentration of X uM with an estimated plasma half-life of Y hr."

2. The firm should include the following statements in the labeling under the Pharmacokinetic Section until such time accurate information is available.

The extent of accumulation of ribavirin following inhalation therapy, as prescribed in the DOSAGE AND ADMINISTRATION Section, is not well defined. Accumulation of ribavirin administered via an endotracheal tube however occurred when 8 hour treatments were given for 3 days. The extent of ribavirin protein binding and its disposition kinetics have not been characterized.

V. RECOMMENDATION

The NDA 18-859 submissions, which were filed both on June 18, 1985 and on November 4, 1983 by Viratek, are approvable by the Division of Biopharmaceutics for inhalation therapy in that the in-vivo bioavailability/bioequivalent (BA/BE) requirement can be DEFERRED under Section 21 CFR 320.22 (e) of Agency's BA/BE requirements (i.e. for good cause). However, the firm should agree in writing to conduct a well-controlled study(ies) to better define this drug's inhalation pharmacokinetics in the intended patient population in order to support the drug's labeling. It is recommended that the firm consult with the Division of Biopharmaceutics to discuss the protocol(s) for such a study(ies) prior to initiation. The overall deficiencies #1 and 2, comments #1 and 2, plus this recommendation should be communicated to the firm.

Tsung Eng Ong Chen

T.E. Mary Ong-Chen, Biochemist
Pharmacokinetic Evaluation Branch

RD Initialed by John P. Hunt
FT Initialed by C.T. Vishwanathan, Ph.D. CTV 8/27/85

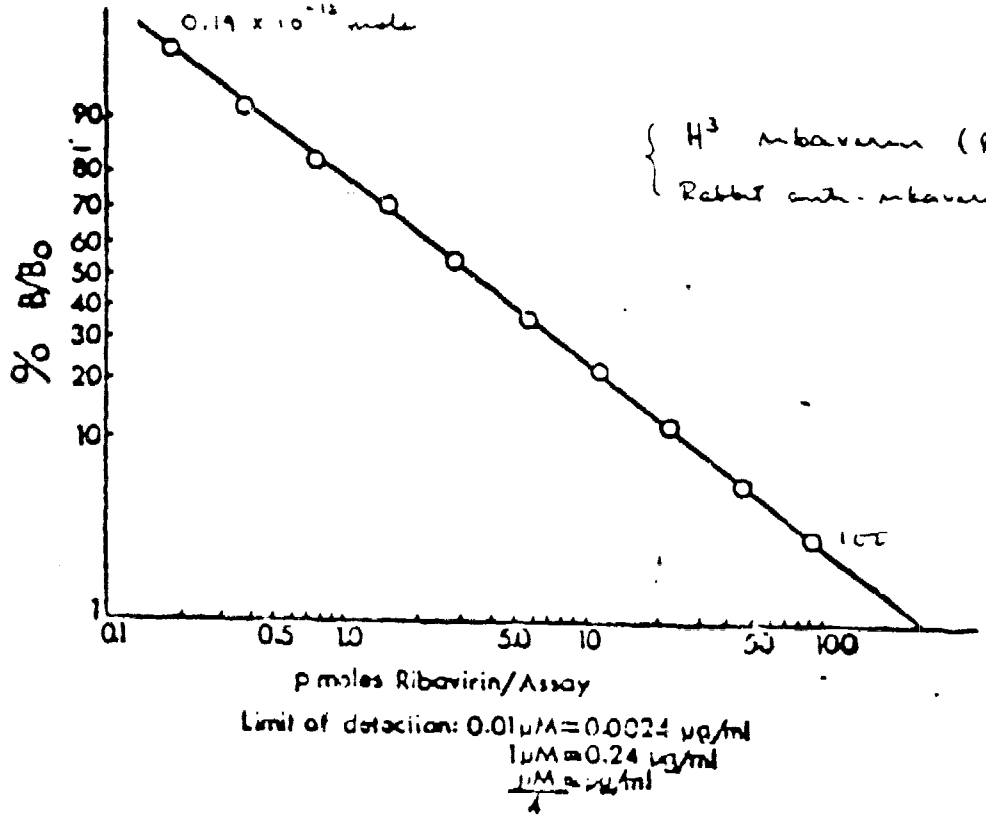
cc: NDA 18-859 Orig.; HFN-815 (Tabor); HFN-225 (Chen); Chron, Division, Drug & Review Files.

TOC:smj:dea:[redacted](08/27/85)

# Appendix A

FIGURES AND TABLES

# RIBAVIRIN STANDARD CURVE




Limit of detection: 0.01 μM = 0.0024 μg/ml
1 μM = 0.24 μg/ml
$\frac{1}{4}$ μM = μg/ml

FIGURE 1.

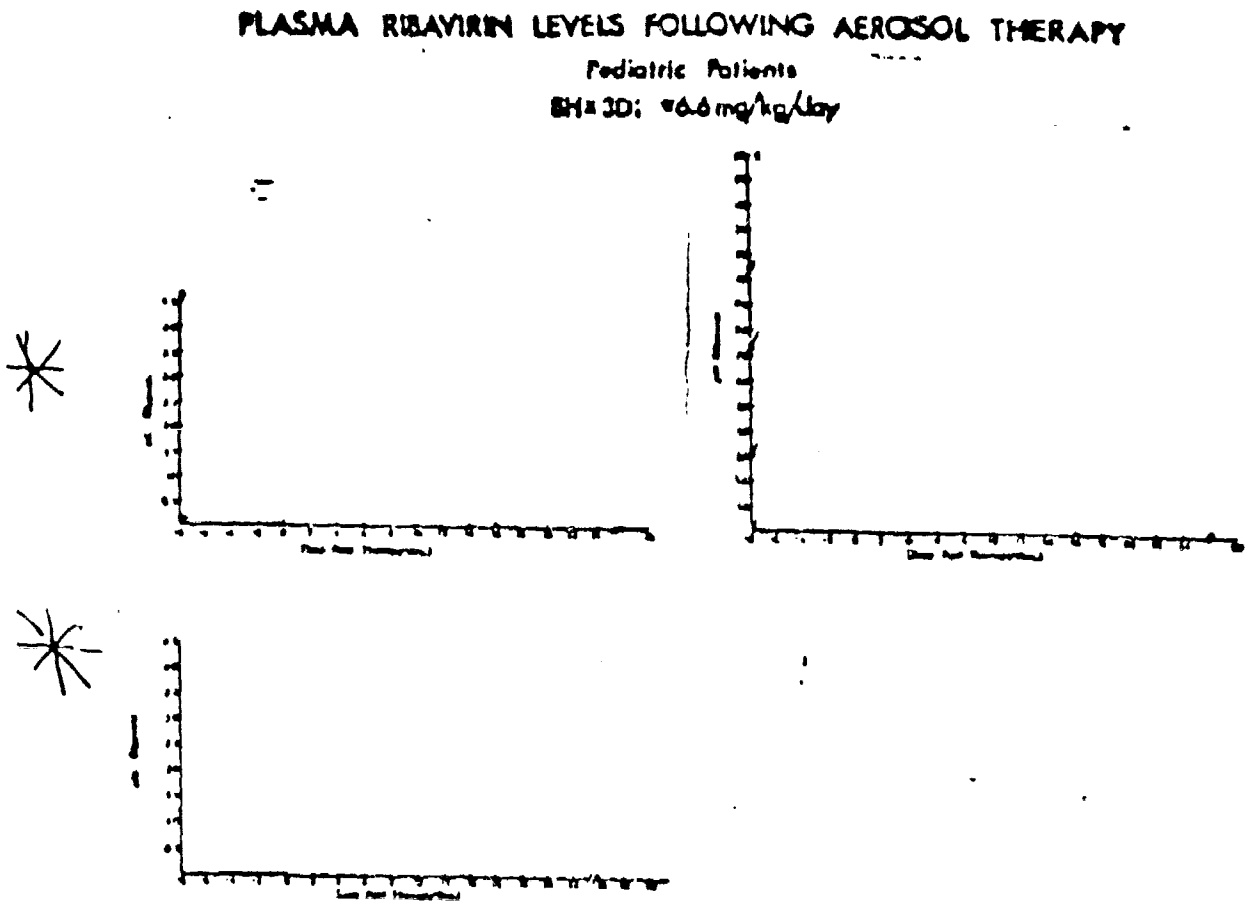



FIGURE 5.

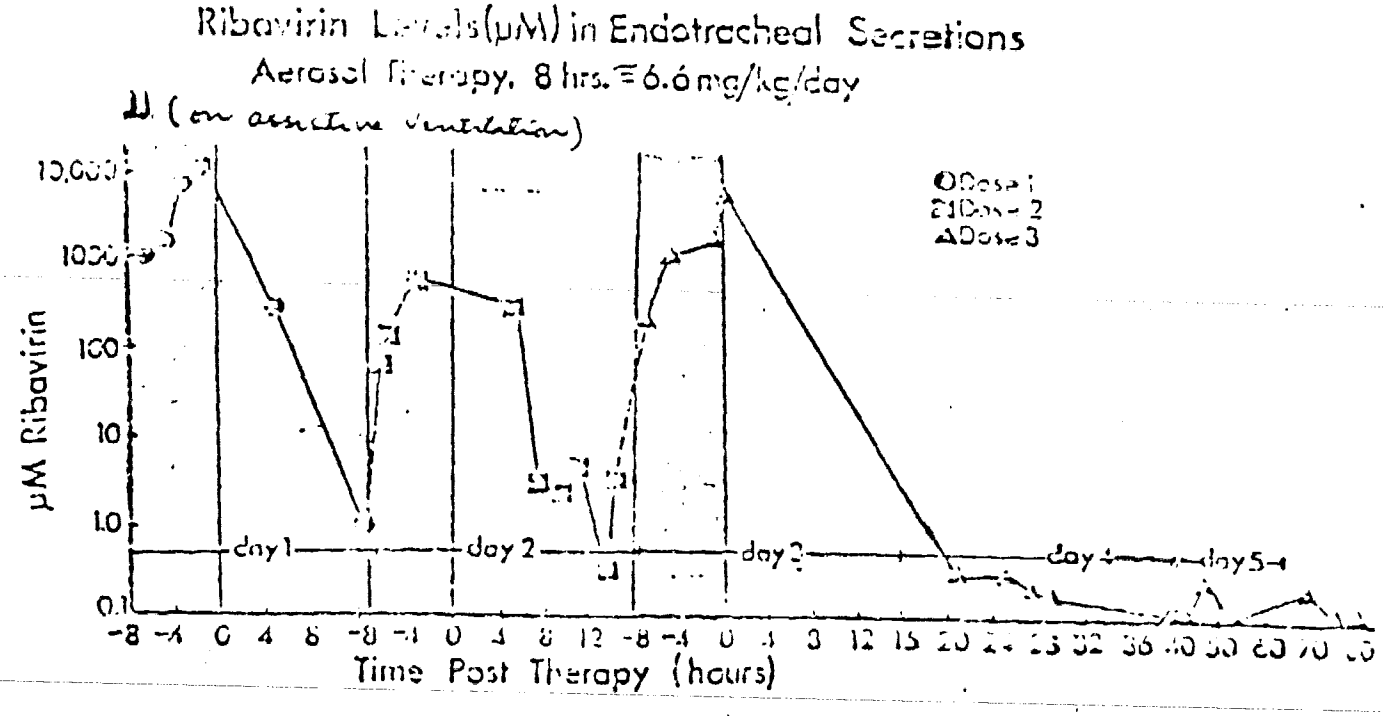



FIGURE 6.

Plasma Ribavirin Levels During
Long Term Therapy ≤20 hrs/dose x 26 days

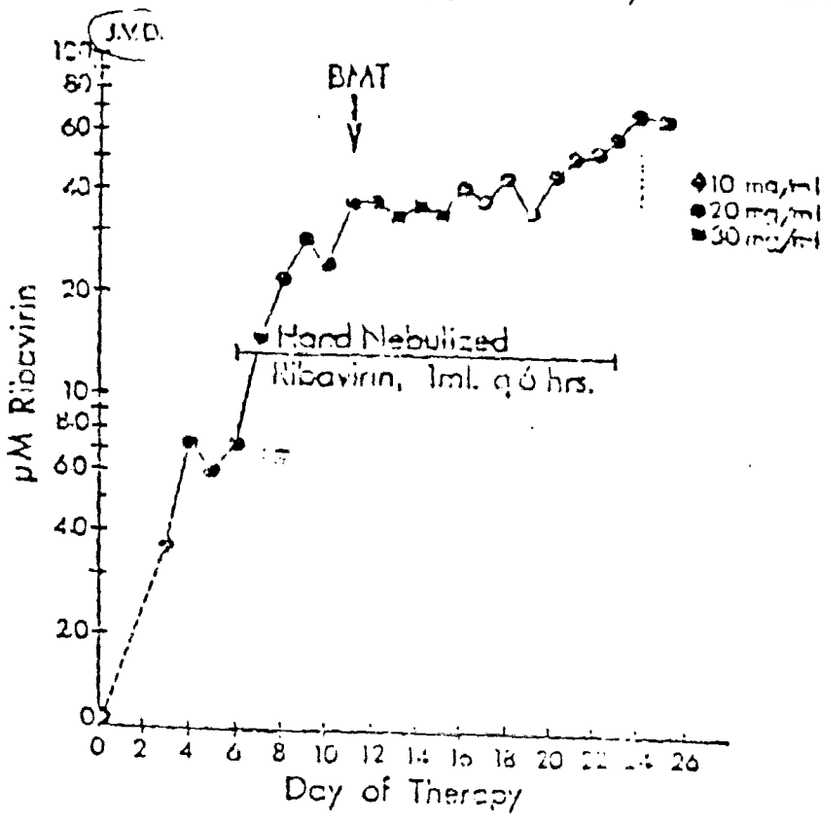



FIGURE 9.

TABLE V.

PEDIATRIC PATIENTS
SHORT-TERM AEROSOL RIBAVIRIN THERAPY

| PATIENT | AGE | SEX | DIAGNOSIS | THERAPY DURATION | ROUTE OF ADMINISTRATION | VIRAL CULTURE |
|---|---|---|---|---|---|---|
| [redacted] | 6 MO | F | BRONCHIOLITIS -- RESPIRATORY FAILURE | 5 H X 3 D | ET | NEG |
| | 5 MO | M | BRONCHIOLITIS | 5 H X 2 D | MASK | ADENO 1 |
| | 2 1/12 YR | M | CROUP ------- RESPIRATORY FAILURE | 5 H X 3 D | ET | NEG (TITER RISE MYCOPLASMA |
| | 17 YR | F | CYSTIC FIBROSIS PNEUMONIA | 5 H X 3 D | MASK | NEG |

TABLE VI.

PEDIATRIC PATIENTS
SHORT-TERM AEROSOL RIBAVIRIN THERAPY

| PATIENT | AGE | SEX | DIAGNOSIS | THERAPY DURATION | ROUTE OF ADMINISTRATION | VIRAL CULTURE |
|---|---|---|---|---|---|---|
| [redacted] | 2 MO | F | BRONCHIOLITIS | 3 H X 1 D | ET* | RSV |
| | 2 MO | F | BRONCHIOLITIS | 8 H X 3 D | ET | RSV |
| | 2 WK | F | BRONCHIOLITIS | 8 H X 3 D | ET | PERTUSSIS |
| | 2 MO | M | BRONCHIOLITIS | 8 H X 3 D | MASK | NEG |

* AEROSOL THERAPY WAS DISCONTINUED AFTER 3 HRS.

TABLE VII.

## PLASMA PHARMACOKINETICS

### INCREASING DURATION OF AEROSOL THERAPY

| DURATION OF THERAPY | MEAN PEAKS* (± SD) µM RIBAVIRIN† | RANGE µM RIBAVIRIN |
|---|---|---|
| 2½ H | 0.76 ± 0.52 | |
| 5 H | 1.1 ± 0.28 | |
| 8 H | 4.4 ± 3.8 | |

* 2-3 DAYS OF AEROSOL TREATMENT

† 1 µM = 0.24 µG/ML

TABLE VIII.

## PLASMA PHARMACOKINETICS

### INCREASING DURATION OF AEROSOL THERAPY

| DURATION OF THERAPY | MEAN PEAK (± SD), µM RIBAVIRIN† | | |
|---|---|---|---|
| | DOSE #1 (DAY 1) | DOSE #2 (DAY 2) | DOSE #3 (DAY 3) |
| 2½ H | 0.60 ± 0.36 | 1.1 ± 0.98 | 1.0 ± 0.71 |
| 5 H | 1.3 ± 0.48 | 1.4 ± 0.07 | 1.1 ± 0.81 |
| 8 H | 3.3 ± 0.91 | 3.5 ± 3.0 | 6.1 ± 7.7 |

†1 µM = 0.24 µG/ML

TABLE XI.

PEDIATRIC PATIENTS[1]
LONG-TERM AEROSOL THERAPY
~20 H/DOSE X 5 DOSES, 20 MG/ML

| PATIENT(S) | AGE | ROUTE OF ADMINISTRATION | PLASMA RIBAVIRIN LEVELS μM MEAN ± SD | RANGE |
|---|---|---|---|---|
| J. [redacted] | 2 MO | RESPIRATOR | 13.2 ± 6.3 | [redacted] |
| [redacted][2] | 3½ YR | FACE MASK | 2.7 ± 0.87 | |
| (1ST COURSE) | 5 MO | MIST TENT | 8.1 ± 2.8 | |
| (2ND COURSE)[3] | 5½ MO | MIST TENT | 9.5 ± 3.9 | |
| [redacted][4] | 8 MO | RESPIRATOR | -- | |

[1] [redacted], COURTESY OF DR. [redacted].

[2] PATIENT RECEIVED 6 DAYS OF THERAPY.

[3] PRE-2ND COURSE OF THERAPY LEVEL OF 2.7 μM, 8 DAYS AFTER LAST DOSE OF 1ST COURSE OF THERAPY

[4] PATIENT ADMITTED TO THERAPY WITH LIVER FAILURE.

TABLE XIII.

IN VITRO ANTIVIRAL ACTIVITY OF RIBAVIRIN

Appendix B

FINAL

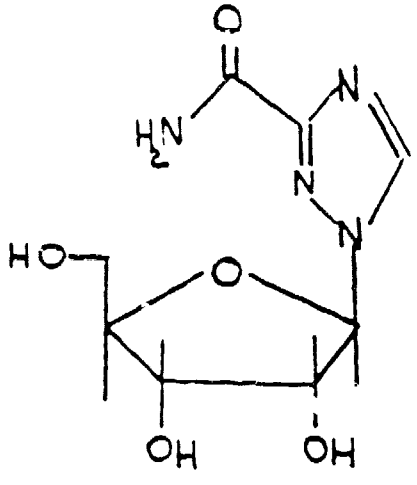
PACKAGE INSERT

# VIRAZOLE$^{R}$ (ribavirin) Aerosol

## DESCRIPTION

Virazole$^{R}$ (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Following oral dosing of 1000 mg/day in four subjects, plasma concentrations of ribavirin ranged from 1.7-5.3 uM after 2.5 hours with a mean concentration of 3.1 uM.

In an intravenous study, a 1000 mg dose of ribavirin was given on day one followed by 1000 mg every 6 hours on days 1-4 and 500 mg every 8 hours on days 5-10. The mean plasma concentrations were 94 uM for 8 subjects with the 1000 mg dose and 68 uM for 11 subjects with the 500 mg dose.

Three patients inhaling aerosolized ribavirin for 2.5 hours each day for three days had a mean peak of 0.76 uM ribavirin in plasma with a plasma half-life of 9-10 hours. Inhalation therapy of five hours duration for each day for 3 days yielded a mean peak of 1.1 uM ribavirin in plasma with a plasma half-life of 6.5-11.0 hours (3 subjects). Ribavirin aerosol therapy for 8 hours a day each day for 3 days gave a mean peak of 4.4 uM ribavirin (3 subjects). Accumulation of ribavirin occurred when 8 hour treatments were given for 3 days.

Concentrations of ribavirin in tracheal secretions were measured in patients following 5-8 hours of aerosolized ribavirin therapy for each of 3 days. Peak values of ribavirin were 1000-7000 uM.

In 5 patients treated with ribavirin aerosol for 20 hours a day for each of 5 days, the mean peak plasma levels of ribavirin ranged from 2.7 uM to 13.2 uM. Ribavirin concentration in respiratory secretions ranged from 1250-113,000 uM during therapy and had peaks ranging from 1250-28,200 uM at the end of therapy.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. Similarly, the bioavailability of the impurities is unknown. After aerosol treatment, peak plasma concentrations are less than the concentration required to reduce by 85-98% plaque formation <u>in vitro</u> by respiratory syncytial virus. After aerosol treatment, respiratory tract secretions contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, respiratory syncytial virus is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

Diagnosis:

Respiratory syncytial virus infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence [3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS

Ribavirin is indicated for lower respiratory tract infection due to RSV only in infants and young children. Respiratory tract infection due to RSV is self-limited in girls and women of childbearing age and ribavirin is not indicated. Ribavirin may cause fetal harm if administered to a pregnant girl or woman. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in adults with chronic obstructive lung disease or asthma. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Deterioration of respiratory function has been associated with ribavirin use in infants. Respiratory function should be carefully monitored during treatment. If respiratory function suddenly deteriorates upon ribavirin administration, treatment should be stopped. After recovery, further treatment should be attempted only with extreme caution and continuous monitoring.

Carcinogenesis, mutagenesis, impairment of fertility: Ribavirin induces cell transformation in an in vitro mammalian system (Balb/C 3T3 cell line). However, in vivo carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: See "Contraindications."

Ribavirin is toxic to lactating animals and their offspring.

ADVERSE REACTIONS

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. In infants, ribavirin aerosol use has rarely been associated with worsening of signs of respiratory tract disease, pneumothorax, rash and reticulocytosis.

Anemia, which occurs frequently with oral and intravenous ribavirin, has not been shown to be associated with use of the aerosol.

Carcinogenesis, mutagenesis, impairment of fertility: Ribavirin induces cell transformation in an in vitro mammalian system (Balb/C 3T3 cell line). However, in vivo carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

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Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: See "Contraindications."

Ribavirin is toxic to lactating animals and their offspring.

ADVERSE REACTIONS

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. In infants, ribavirin aerosol use has rarely been associated with worsening of signs of respiratory tract disease, pneumothorax, rash and reticulocytosis.

Anemia, which occurs frequently with oral and intravenous ribavirin, has not been shown to be associated with use of the aerosol.

HOW SUPPLIED

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C(59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded daily. Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

REFERENCES:

1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. Antimicrob Agents Chemother 17:770-775,1 1980.

2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., RG. In vivo inhibition of respiratory syncytial virus by ribavirin. Antimicrob Agents Chemother 21:125-130, 1982.

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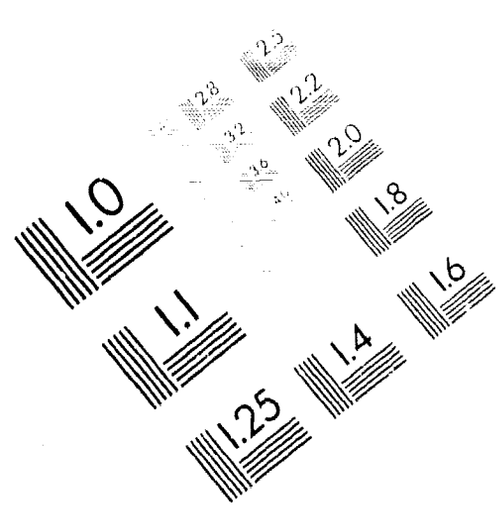
5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. J Clin Microbiol 16:329-33, 1982.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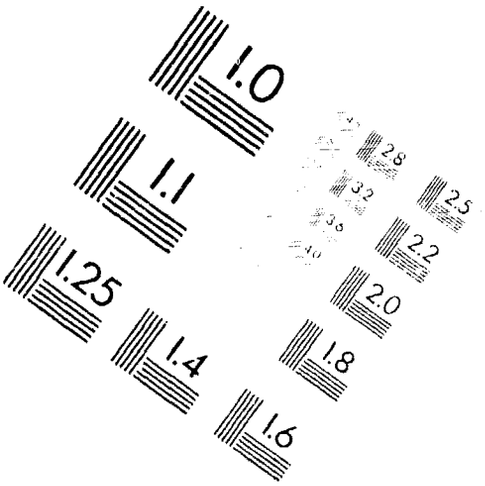
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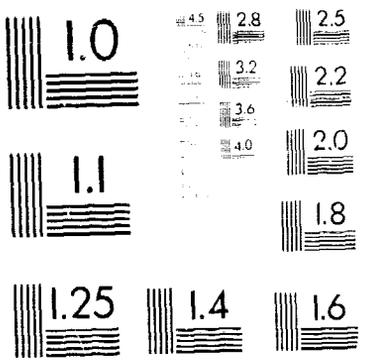
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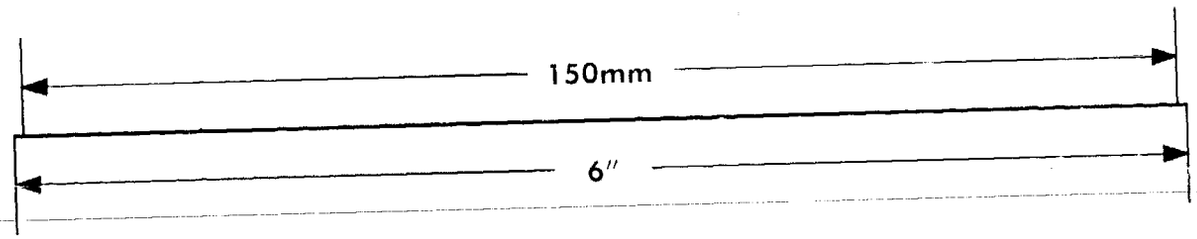
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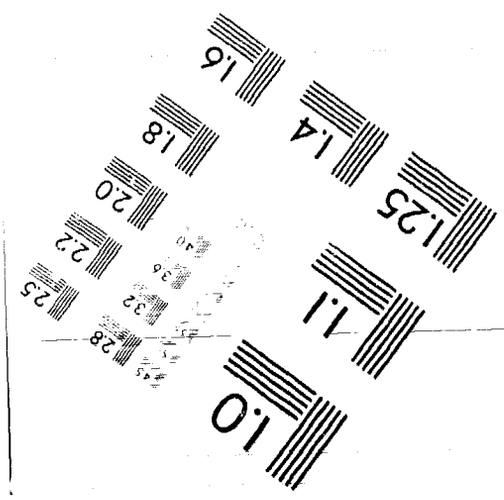
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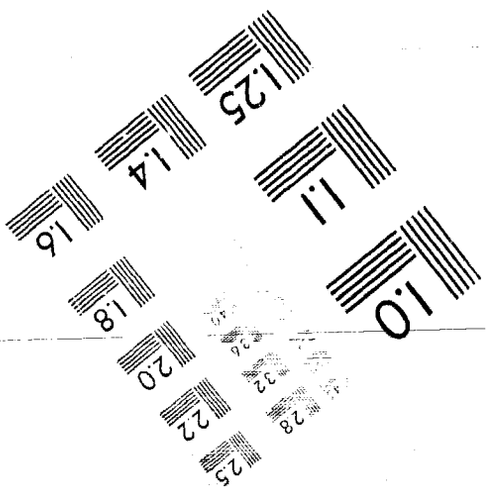
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# Virazole®
## (Ribavirin)

PRESCRIBING INFORMATION

**WARNING:**

**RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.** Conditions for safe use with a ventilator are still in development.

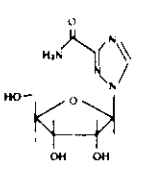
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

**DESCRIPTION:**

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

**CLINICAL PHARMACOLOGY:**

**Antiviral effects:**

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

**Immunologic effects:**

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

**Microbiology:**

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

**Pharmacokinetics:**

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μM, with a mean concentration of 0.76 μM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 μM, with a mean concentration of 6.8 μM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

**INDICATIONS AND USAGE:**

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

**Diagnosis:**

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

**CONTRAINDICATIONS:**

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

**WARNINGS:**

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

**PRECAUTIONS:**

**General:**

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

**Drug Interactions:**

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

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Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

# Virazole®
## (Ribavirin)

lyophilized for aerosol administration

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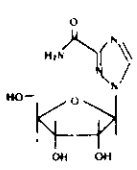

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The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

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**CONTRAINDICATIONS:**

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

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Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

**PRECAUTIONS:**

**General:**

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

**Drug Interactions:**

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

**Carcinogenesis, mutagenesis, impairment of fertility:**

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

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Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

**Pregnancy:**

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

**ADVERSE REACTIONS:**

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

**DOSAGE AND ADMINISTRATION**

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection. Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation, in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

**HOW SUPPLIED:**

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solution which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.


**REFERENCES:**

1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. *Antimicrob Agents Chemother* 17:770-775, 1980.
2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., RG. *In vivo* inhibition of respiratory syncytial virus by ribavirin. *Antimicrob Agents Chemother* 21:125-130, 1982.
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**ICN Pharmaceuticals, Inc.**

ICN PLAZA
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
(714) 545-0100



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VIRATEK
A nucleic acid development company

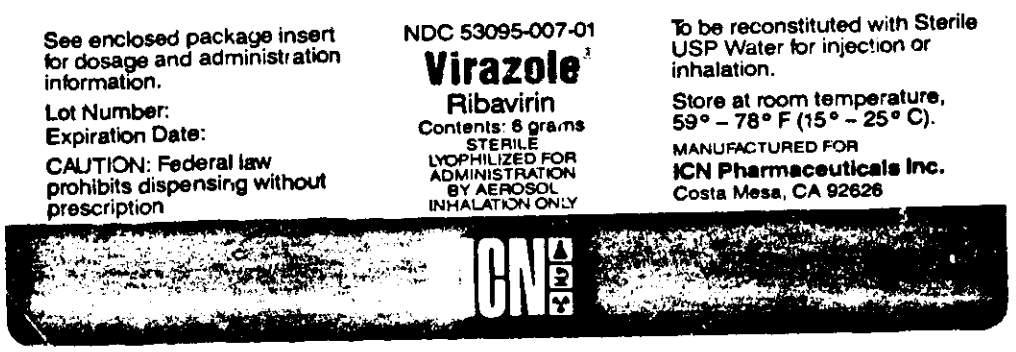
CONFIDENTIAL

# VIRAZOLE® (RIBAVIRIN) AEROSOL, QUARTERLY REPORT

## October 1, 1987 - December 31, 1987

(c) LABELING - Vial Label

No changes were made during the period covered by this report.



# Virazole®
## (Ribavirin)

*Lyophilized powder for aerosol administration*

## PRESCRIBING INFORMATION

**WARNING:**

**RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.** Conditions for safe use with a ventilator are still in development.

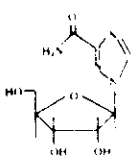
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

### DESCRIPTION:

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

### CLINICAL PHARMACOLOGY:

#### Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

#### Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

#### Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16µg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

#### Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 µM, with a mean concentration of 0.76 µM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 µM, with a mean concentration of 6.8 µM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

### INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

#### Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

### CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

### WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 56 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

### PRECAUTIONS:

#### General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

#### Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

#### Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin treated animals (male or female) has not been adequately investigated.

**Pregnancy:**

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

**ADVERSE REACTIONS:**

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

**DOSAGE AND ADMINISTRATION**

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

**HOW SUPPLIED:**

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

**REFERENCES:**


1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. *Antimicrob Agents Chemother* 17:770-775, 1 1980.
2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., KG. *In vivo* inhibition of respiratory syncytial virus by ribavirin. *Antimicrob Agents Chemother* 21:125-130, 1982.
3. Taber LH, Knight V, Gilbert BE, McClung HW et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory tract infection in infants. *Pediatrics* 72:613-618, 1983.
4. Hall CB, McBride JT, Walsh EE, Bell DM et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 308:1443-7, 1983.
5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. *J Clin Microbiol* 16:329-33, 1982.



**ICN Pharmaceuticals, Inc.**
ICN PLAZA
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
(714) 545-0100

# VIRAZOLE® (RIBAVIRIN) AEROSOL, QUARTERLY REPORT

## April 1, 1988 to June 30, 1988

(c) LABELING - Vial Label

No changes were made during the period covered by this report.

See enclosed package insert for dosage and administration information.

Lot Number:

Expiration Date:

CAUTION: Federal law prohibits dispensing without prescription

NDC 53095-007-01

Virazole

Ribavirin

Contents: 6 grams

STERILE LYOPHILIZED FOR ADMINISTRATION BY AEROSOL INHALATION ONLY

To be reconstituted with sterile USP Water for injection or inhalation.

Store at room temperature, 59° - 76° F (15° - 25° C).

MANUFACTURED FOR

**ICN Pharmaceuticals Inc.**

Costa Mesa, CA 92626

ICN

# Virazole®
## (Ribavirin)

PRESCRIBING INFORMATION

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Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

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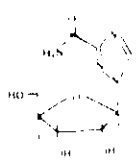

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It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

**INDICATIONS AND USAGE:**

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

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Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

**Diagnosis:**

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

**CONTRAINDICATIONS:**

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

**WARNINGS:**

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

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**PRECAUTIONS:**

**General:**

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

**Drug Interactions:**

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

**Carcinogenesis, mutagenesis, impairment of fertility:**

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 10-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

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**Pregnancy:**

Teratogenic Effects. Pregnancy Category X. See "Contraindications" section.

Nursing Mothers. Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

## ADVERSE REACTIONS:

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Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

## DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[1] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

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## HOW SUPPLIED:

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

## REFERENCES.


1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. *Antimicrob Agents Chemother* 17:770-775, 1 1980.
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3300 HYLAND AVENUE
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1957-02
Rev. 1-88

CONFIDENTIAL

# VIRAZOLE® (RIBAVIRIN) AEROSOL. QUARTERLY REPORT

## July 1, 1988 to September 30, 1988

(c) LABELING - Vial Label

No changes were made during the period covered by this report.

See enclosed package insert for dosage and administration information.

Lot Number:
Expiration Date:

CAUTION: Federal law prohibits dispensing without prescription.

NDC 53095-007-01

**Virazole**™

Ribavirin

Contents: 6 grams

STERILE LYOPHILIZED FOR ADMINISTRATION BY AEROSOL INHALATION ONLY

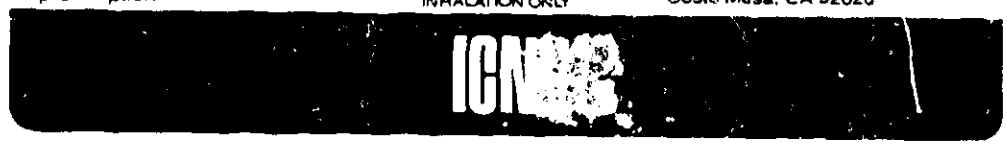
To be reconstituted with Sterile USP Water for injection or inhalation.

Store at room temperature, 59° – 78° F (15° – 25° C).

MANUFACTURED FOR

**ICN Pharmaceuticals Inc.**

Costa Mesa, CA 92626



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## (Ribavirin)

PRESCRIBING INFORMATION

**WARNING:**

**RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.** Conditions for safe use with a ventilator are still in development.

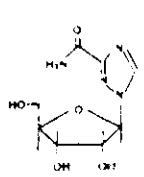
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

**DESCRIPTION:**

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

**CLINICAL PHARMACOLOGY:**

**Antiviral effects:**

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

**Immunologic effects:**

Neutralizing antibody responses to RSV were decreased in ribavirin treated *compared to placebo treated infants.*[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of the *thymus, spleen, and lymph* nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

**Microbiology:**

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16µg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

**Pharmacokinetics:**

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from *0.44 to 1.55 µM, with a mean concentration* of 0.76 µM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 µM, with a mean concentration of 6.8 µM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, *peak plasma concentrations are less than the* concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

**INDICATIONS AND USAGE:**

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory *tract disease or have disease that is* mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

*The presence of an underlying* condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

**Diagnosis:**

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[5] or ELISA[6] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. *Treatment may be initiated while* awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

**CONTRAINDICATIONS:**

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. *The drug causes* embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

**WARNINGS:**

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg *for 30 days. The significance of these find*ings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

**PRECAUTIONS:**

**General:**

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

**Drug Interactions:**

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

**Carcinogenesis, mutagenesis, impairment of fertility:**

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested); but teratogenicity of ribavirin treated animals (male or female) has not been adequately investigated.

**Pregnancy:**

Teratogenic Effects. Pregnancy Category X. See "Contraindications" section.

Nursing Mothers. Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

## ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

## DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[1] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

*Virazole* is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

## HOW SUPPLIED:

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

## REFERENCES:


1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. *Antimicrob Agents Chemother* 17:770-775, 1980.
2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., RG. *In vivo* inhibition of respiratory syncytial virus by ribavirin. *Antimicrob Agents Chemother* 21:125-130, 1982.
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5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. *J Clin Microbiol* 16:329-33, 1982.



ICN Pharmaceuticals, Inc.
ICN PLAZA
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
(714) 545-0100



1957-02
Rev. 1-88

CONFIDENTIAL

# VIRAZOLE® (RIBAVIRIN) AEROSOL, QUARTERLY REPORT

## October 1, 1988 - December 31, 1988

(c) LABELING - Vial Label

No changes were made during the period covered by this report.

See enclosed package insert for dosage and administration information.

Lot Number:

Expiration Date:

CAUTION: Federal law prohibits dispensing without prescription

NDC 53095-007-01

**Virazole** ™

Ribavirin

Contents: 6 grams

STERILE

LYOPHILIZED FOR ADMINISTRATION BY AEROSOL INHALATION ONLY

To be reconstituted with Sterile USP Water for injection or inhalation.

Store at room temperature, 59° - 78° F (15° - 25° C).

MANUFACTURED FOR

**ICN Pharmaceuticals Inc.**

Costa Mesa, CA 92626

ICN

# Virazole®
## (Ribavirin)

PRESCRIBING INFORMATION

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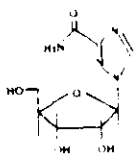
Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

**DESCRIPTION:**

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 109 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



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It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

**INDICATIONS AND USAGE:**

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

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The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

**Diagnosis:**

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[5,6] or ELISA[7] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

**CONTRAINDICATIONS:**

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

**WARNINGS:**

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Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

**PRECAUTIONS:**

**General:**

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

**Drug Interactions:**

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

**Carcinogenesis, mutagenesis, impairment of fertility:**

Ribavirin induces cell transformation in an *in vitro* mammalian system (BalbC 3T3

cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

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**Pregnancy:**

Teratogenic Effects. Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

## ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

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Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

## DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding new, reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

## HOW SUPPLIED:

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

## REFERENCES:


1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus in vitro. *Antimicrob Agents Chemother* 17:770-775, 1 1980.
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**ICN Pharmaceuticals, Inc.**
ICN PLAZA
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
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*95?-02
Rev. 1-83

VIRATEK
A nucleic acid development company

February 20, 1990





Food and Drug Administration
Division of Antiviral Drug Products, HFD-530
Attention: Document Control Room 15B41
5600 Fishers Lane
Rockville, Maryland 20857

**RE: NDA 18,859**
**VIRAZOLE (RIBAVIRIN) AEROSOL**
**ANNUAL REPORT**

Gentlemen:

Pursuant to 21 CFR 314.81, we are pleased to enclose our Annual Report for NDA 18,859, Virazole (Ribavirin) Aerosol for January 1, 1989 to December 31, 1989.

Sincerely,

Alice M. Wei
Manager, U.S. Regulatory Affairs

Enclosure

# Virazole®
## (Ribavirin)

PRESCRIBING INFORMATION

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**RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT.** Conditions for safe use with a ventilator are still in development.

Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

**DESCRIPTION:**

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:

Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$, and the molecular weight is 244.2 Daltons.

**CLINICAL PHARMACOLOGY:**

**Antiviral effects:**

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

**Immunologic effects:**

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

**Microbiology:**

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16µg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

**Pharmacokinetics:**

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 µM, with a mean concentration of 0.76 µM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.2 µM, with a mean concentration of 6.8 µM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

**INDICATIONS AND USAGE:**

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[4,5] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[5]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

**Diagnosis:**

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[4,5] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

**CONTRAINDICATIONS:**

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

**WARNINGS:**

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

**PRECAUTIONS:**

**General:**

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

**Drug Interactions:**

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

**Carcinogenesis, mutagenesis, impairment of fertility:**

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3

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(cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

**Pregnancy:**

Teratogenic Effects. Pregnancy Category X. See "Contraindications" section.

Nursing Mothers. Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

## ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

**Overdosage:**

No overdosage with ribavirin by aerosol administration has been reported in the human. The $LD_{50}$ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

## DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[1] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

## HOW SUPPLIED:

Virazole (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

## REFERENCES:


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4. Hall CB, McBride JT, Walsh EE, Bell DM, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 308:1443-7, 1983.
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**ICN Pharmaceuticals, Inc.**
ICN PL-2A
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
(714) 545-0100

VIRATEK

A nucleic acid development company

## CONTAINER LABEL

See enclosed package insert for dosage and administration information.

Lot Number:
Expiration Date:

CAUTION: Federal law prohibits dispensing without prescription

NDC 53095-007-01

Ribavirin
Contents 6 grams
STERILE
LYOPHILIZED FOR ADMINISTRATION BY AEROSOL INHALATION ONLY

To be reconstituted with Sterile USP Water for injection or inhalation.

Store at room temperature. 59° - 78° F (15° - 25° C)

MANUFACTURED FOR
**ICN Pharmaceuticals Inc.**
Costa Mesa, CA 92626

ICN

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