CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)
20-438/S-001

Trade Name: Vesanoid Capsules

Generic Name(s): (tretinoin)

Sponsor: Hoffman-La Roche, Inc.
Agent:

Approval Date: February 14, 2000

Indication: Provides for Geriatric Use subsection under Precautions

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-438/S-001

Approval Letter

Div File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-438/S-001

FEB 14 2000

Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug application dated August 18, 1999, received August 19, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VESANOID (tretinoin) Capsules, 10 mg.

This supplemental new drug application provides for a "Geriatric Use" subsection under the PRECAUTIONS section of the package insert in accordance with 21 CFR 201.57 (f)10. Additionally, as recommended in our March 8, 1999 letter, it contains minor terminology changes to the PHARMACOKINETICS section for cytochrome P450 enzymes.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the August 18, 1999 draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-438/S-001." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

/S/ 2/14/00

Robert L. Justice, M.D.
Deputy Director
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CC:
Archival NDA 20-438/SLR-001
HFD-150/Div. Files
HFD-150/M.Pelosi
HFD-150/ Rahman/2-7-00
Hirschfeld/2-7-00
Johnson/2-11-00
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: map/February 4, 2000
Initialed by:Pease
final:Pelosi/ 2-11-00
filename: NDA/20438/ SLR001/Geriatric_AP

S

2-14-00

APPROVAL (AP)

Div File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-438/S-001

Hoffman-La Roche, Inc.
340 King Street
Nutley, NJ 07110-1199

JUN 29 2000

Attention: Lynn De Venezia-Tobias
Program Manager, Regulatory Affairs

Dear Ms. De Venezia-Tobias:

We acknowledge the receipt of your June 8, 2000 submission containing final printed labeling in response to our February 14, 2000 letter approving your supplemental new drug application for Vesanoid (tretinoin) Capsules.

We have reviewed the labeling that you submitted in accordance with our February 14, 2000 letter, and we find it acceptable. However, that in the section CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions, the comma after "*CYP*" should be removed at the next printing. The sentence should read as follows:

> "The precise cytochrome P450 enzymes involved in these interactions have not been specified; *CYP* 3A4, 2C8 and 2E have been implicated in various preliminary reports."

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

S 6-29-00

Richard Pazdur, M.D.
Director
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-438
HFD-150/Div. Files
HFD-150/M.Pelosi
HFD-150/ John Johnson
S. Hirschfeld
A. Rahman
J. Duan

HF-2/Medwatch (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

Drafted by: mp/June 27, 2000
Initialed by Pease: June 27, 2000
Final by Pelosi:June 28, 2000

filename: NDA/20438/SLR001/FA_slr001_AR

ACKNOWLEDGE AND RETAIN (AR)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-438/S-001

Final Printed Labeling

FINAL PRINTED LABELING
PACKAGE INSERT

NDA NO. [illegible] Reviewed by: [illegible] 6.27.00

Roche

VESANOID®
(tretinoin)
CAPSULES

WARNINGS:

1. ***Experienced Physician and Institution:*** Patients with acute promyelocytic leukemia (APL) are at high risk in general and can have severe adverse reactions to VESANOID (tretinoin). VESANOID should therefore be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia and in a facility with laboratory and supportive services sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity, including respiratory compromise. Use of VESANOID requires that the physician concludes that the possible benefit to the patient outweighs the following known adverse effects of the therapy.
2. ***Retinoic Acid-APL Syndrome:*** About 25% of patients with APL treated with VESANOID have experienced a syndrome called the retinoic-acid-APL (RA-APL) syndrome characterized by fever, dyspnea, weight gain, radiographic pulmonary infiltrates and pleural or pericardial effusions. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. It has been observed with or without concomitant leukocytosis. Endotracheal intubation and mechanical ventilation have been required in some cases due to progressive hypoxemia, and several patients have expired with multiorgan failure. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of VESANOID.

   The management of the syndrome has not been defined rigorously, but high-dose steroids given at the first suspicion of the RA-APL syndrome appear to reduce morbidity and mortality. At the first signs suggestive of the syndrome (unexplained fever, dyspnea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities), high-dose steroids (dexamethasone 10 mg intravenously administered every 12 hours for 3 days or until the resolution of symptoms) should be immediately initiated, irrespective of the leukocyte count. The majority of patients do not require termination of VESANOID therapy during treatment of the RA-APL syndrome.
3. ***Leukocytosis at Presentation and Rapidly Evolving Leukocytosis During VESANOID Treatment:*** During VESANOID treatment about 40% of patients will develop rapidly evolving leukocytosis. Patients who present with high WBC at diagnosis (>$5x10^9$/L) have an increased risk of a further rapid increase in WBC counts. Rapidly evolving leukocytosis is associated with a higher risk of life-threatening complications.

   If signs and symptoms of the RA-APL syndrome are present together with leukocytosis, treatment with high-dose steroids should be initiated immediately. Some investigators routinely add chemotherapy to VESANOID treatment in the case of patients presenting with a WBC count of >$5x10^9$/L or in the case of a rapid increase in WBC count for patients leukopenic at start of treatment, and have reported a lower incidence of the RA-APL syndrome. Consideration could be given to adding full-dose chemotherapy (including an anthracycline if not contraindicated) to the VESANOID therapy on day 1 or 2 for patients presenting with a WBC count of >$5x10^9$/L, or immediately, for patients presenting with a WBC count of <$5x10^9$/L, if the WBC count reaches ≥$6x10^9$/L by day 5, or ≥$10x10^9$/L by day 10, or ≥$15x10^9$/L by day 28.
4. ***Teratogenic Effects. Pregnancy Category D – see WARNINGS:*** There is a high risk that a severely deformed infant will result if VESANOID is administered during pregnancy. If, nonetheless, it is determined that VESANOID represents the best available treatment for a pregnant woman or a woman of childbearing potential, it must be assured that the patient has received full information and warnings of the risk to the fetus if she were to be pregnant and of the risk of possible contraception failure and has been instructed in the need to use two reliable forms of contraception simultaneously during therapy and

(Continued)

WARNINGS: *(Continued)*

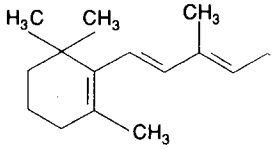
for 1 month following discontinuation
edged her understanding of the need
unless abstinence is the chosen metho

Within 1 week prior to the institution of
should have blood or urine collected f
test with a sensitivity of at least 50 mIU
therapy should be delayed until a ne
obtained. When a delay is not possible
on two reliable forms of contraception.
ception counseling should be repeated
of VESANOID treatment.

DESCRIPTION: VESANOID (tretinoin) is a
of acute promyelocytic leukemia (APL) cel
10 mg soft gelatin capsule for oral adminis
tains beeswax, butylated hydroxyanisole,
soybean oil flakes, hydrogenated vegetable
capsule shell contains glycerin, yellow iro
dioxide, methylparaben and propylparaben.

Chemically, tretinoin is all-*trans* retinoic acid a
It is a yellow to light orange crystalline powder

The structural formula is as follows:



CLINICAL PHARMACOLOGY: ***Mechanis***
cytolytic agent but instead induces cytodiffer
ation of APL cells in culture and in vivo. In
produces an initial maturation of the primitive
leukemic clone, followed by a repopulation o
al blood by normal, polyclonal hematopoietic
plete remission (CR). The exact mechanism
unknown.

Pharmacokinetics: Tretinoin activity is prim
human pharmacokinetics studies, orally
absorbed into the systemic circulation, with
administered radiolabel recovered in the urin
life of tretinoin following initial dosing is 0.5
There is evidence that tretinoin induces its o
concentrations decrease on average to one-t
1 week of continuous therapy. Mean ± SD
decreased from 394 ± 89 to 138 ± 139 ng/
(AUC) values decreased from 537 ± 191 ng·
ing 45 mg/m² daily dosing in 7 APL patients.
for this change has not increased response.

Absorption: A single 45 mg/m² (~80 mg) ora
in a mean ± SD peak tretinoin concentratio
reach peak concentration was between 1 an

Distribution: The apparent volume of distrib
determined. Tretinoin is greater than 95% bo
albumin. Plasma protein binding remains c
range of 10 to 500 ng/mL.

Metabolism: Tretinoin metabolites have been
Cytochrome P450 enzymes have been imp
lism of tretinoin. Metabolites include 13-*cis* r
acid, 4-oxo *cis* retinoic acid, and 4-oxo *trans*
patients, daily administration of a 45 mg/m²
approximately tenfold increase in the urinary
acid glucuronide after 2 to 6 weeks of contin
baseline values.

Excretion: Studies with radiolabeled drug ha
oral administration of 2.75 and 50 mg doses
the radioactivity was recovered in the urine ar
3 subjects, approximately 63% of radioactiv
within 72 hours and 31% appeared in the fec

Special Populations: The pharmacokinetics o
rately evaluated in women, in members of di
viduals with renal or hepatic insufficiency.

Drug-Drug Interactions: In 13 patients wh
tretinoin for 4 consecutive weeks, administ
1200 mg oral dose) 1 hour prior to the admin
day 29 led to a 72% increase (218 ± 224 vs
mean plasma AUC. The precise cytochron
these interactions have not been specified;
been implicated in various preliminary reports

VESANOID®
(tretinoin)
CAPSULES
XXXXXXXX

VESANOID®
(tretinoin)
CAPSULES
XXXXXXXX

WARNINGS: *(Continued)*

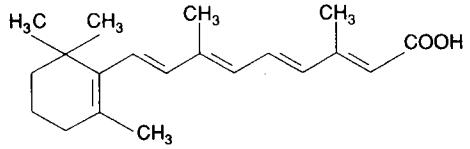
for 1 month following discontinuation of therapy, and has acknowledged her understanding of the need for using dual contraception, unless abstinence is the chosen method.

Within 1 week prior to the institution of VESANOID therapy, the patient should have blood or urine collected for a serum or urine pregnancy test with a sensitivity of at least 50 mIU/L. When possible, VESANOID therapy should be delayed until a negative result from this test is obtained. When a delay is not possible, the patient should be placed on two reliable forms of contraception. Pregnancy testing and contraception counseling should be repeated monthly throughout the period of VESANOID treatment.

DESCRIPTION: VESANOID (tretinoin) is a retinoid that induces maturation of acute promyelocytic leukemia (APL) cells in culture. It is available in a 10 mg soft gelatin capsule for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils and soybean oil. The gelatin capsule shell contains glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben and propylparaben.

Chemically, tretinoin is all-*trans* retinoic acid and is related to retinol (Vitamin A). It is a yellow to light orange crystalline powder with a molecular weight of 300.44.

The structural formula is as follows:



CLINICAL PHARMACOLOGY: ***Mechanism of Action:*** Tretinoin is not a cytolytic agent but instead induces cytodifferentiation and decreased proliferation of APL cells in culture and in vivo. In APL patients, tretinoin treatment produces an initial maturation of the primitive promyelocytes derived from the leukemic clone, followed by a repopulation of the bone marrow and peripheral blood by normal, polyclonal hematopoietic cells in patients achieving complete remission (CR). The exact mechanism of action of tretinoin in APL is unknown.

Pharmacokinetics: Tretinoin activity is primarily due to the parent drug. In human pharmacokinetics studies, orally administered drug was well absorbed into the systemic circulation, with approximately two-thirds of the administered radiolabel recovered in the urine. The terminal elimination half-life of tretinoin following initial dosing is 0.5 to 2 hours in patients with APL. There is evidence that tretinoin induces its own metabolism. Plasma tretinoin concentrations decrease on average to one-third of their day 1 values during 1 week of continuous therapy. Mean ± SD peak tretinoin concentrations decreased from 394 ± 89 to 138 ± 139 ng/mL, while area under the curve (AUC) values decreased from 537 ± 191 ng·h/mL to 249 ± 185 ng·h/mL during 45 mg/m² daily dosing in 7 APL patients. Increasing the dose to "correct" for this change has not increased response.

Absorption: A single 45 mg/m² (~80 mg) oral dose to APL patients resulted in a mean ± SD peak tretinoin concentration of 347 ± 266 ng/mL. Time to reach peak concentration was between 1 and 2 hours.

Distribution: The apparent volume of distribution of tretinoin has not been determined. Tretinoin is greater than 95% bound in plasma, predominately to albumin. Plasma protein binding remains constant over the concentration range of 10 to 500 ng/mL.

Metabolism: Tretinoin metabolites have been identified in plasma and urine. Cytochrome P450 enzymes have been implicated in the oxidative metabolism of tretinoin. Metabolites include 13-*cis* retinoic acid, 4-oxo *trans* retinoic acid, 4-oxo *cis* retinoic acid, and 4-oxo *trans* retinoic acid glucuronide. In APL patients, daily administration of a 45 mg/m² dose of tretinoin resulted in an approximately tenfold increase in the urinary excretion of 4-oxo *trans* retinoic acid glucuronide after 2 to 6 weeks of continuous dosing, when compared to baseline values.

Excretion: Studies with radiolabeled drug have demonstrated that after the oral administration of 2.75 and 50 mg doses of tretinoin, greater than 90% of the radioactivity was recovered in the urine and feces. Based upon data from 3 subjects, approximately 63% of radioactivity was recovered in the urine within 72 hours and 31% appeared in the feces within 6 days.

Special Populations: The pharmacokinetics of tretinoin have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

Drug-Drug Interactions: In 13 patients who had received daily doses of tretinoin for 4 consecutive weeks, administration of ketoconazole (400 to 1200 mg oral dose) 1 hour prior to the administration of the tretinoin dose on day 29 led to a 72% increase (218 ± 224 vs 375 ± 285 ng·h/mL) in tretinoin mean plasma AUC. The precise cytochrome P450 enzymes involved in these interactions have not been specified; *CYP*, 3A4, 2C8 and 2E have been implicated in various preliminary reports.

VESANOID® (tretinoin)

Clinical Studies: VESANOID has been investigated in 114 previously treated APL patients and in 67 previously untreated ("de novo") patients in one open-label, uncontrolled single investigator clinical study (Memorial Sloan-Kettering Cancer Center [MSKCC]) and in two cohorts of compassionate cases treated by multiple investigators under the auspices of the National Cancer Institute (NCI). All patients received 45 mg/m²/day as a divided oral dose for up to 90 days or 30 days beyond the day that CR was reached. Results are shown in the following table:

	MSKCC		NCI Cohort 1		NCI Cohort 2	
	Relapsed n=20	De Novo n=15	Relapsed* n=48	De Novo n=14	Relapsed n=46	De Novo† n=38
Complete Remission	16 (80%)	11 (73%)	24 (50%)	5 (36%)	24 (52%)	26 (68%)
Median Survival (Mo)	10.8	NR	5.8	0.5	8.8	NR
Median Follow-up (Mo)	9.9	42.9	5.6	1.2	8.0	13.1
RA-APL Syndrome	4 (20%)	5 (33%)	10 (21%)	6 (43%)	NA	NA

NR = Not Reached

NA = Not Available

*Including 9 chemorefractory patients

†Including 8 patients who received chemotherapy but failed to enter remission

The median time to CR was between 40 and 50 days (range: 2 to 120 days). Most patients in these studies received cytotoxic chemotherapy during the remission phase. These results compare to the 30% to 50% CR rate and ≤6 month median survival reported for cytotoxic chemotherapy of APL in the treatment of relapse.

Ten of 15 pediatric cases achieved CR (8 of 10 males and 2 of 5 females). There were insufficient patients of black, Hispanic or Asian derivation to estimate relative response rates in these groups, but responses were seen in each category.

Responses were seen in 3 of 4 patients for whom cytogenetic analysis failed to detect the t(15;17) translocation typically seen in APL. The t(15;17) translocation results in the PML/RARα gene, which appears necessary for this disease. Molecular genetic studies were not conducted in these cases, but it is likely they represent cases with a masked translocation giving rise to PML/RARα. Responses to tretinoin have not been observed in cases in which PML/RARα fusion has been shown to be absent.

INDICATIONS AND USAGE: VESANOID (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), French-American-British (FAB) classification M3 (including the M3 variant), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. VESANOID is for the induction of remission only. The optimal consolidation or maintenance regimens have not been defined, but all patients should receive an accepted form of remission consolidation and/or maintenance therapy for APL after completion of induction therapy with VESANOID.

CONTRAINDICATIONS: VESANOID is contraindicated in patients with a known hypersensitivity to retinoids. VESANOID should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsule.

WARNINGS: ***Pregnancy Category D – see boxed WARNINGS:*** Tretinoin has teratogenic and embryotoxic effects in mice, rats, hamsters, rabbits and pigtail monkeys, and may be expected to cause fetal harm when administered to a pregnant woman. Tretinoin causes fetal resorptions and a decrease in live fetuses in all animals studied. Gross external, soft tissue and skeletal alterations occurred at doses higher than 0.7 mg/kg/day in mice, 2 mg/kg/day in rats, 7 mg/kg/day in hamsters, and at a dose of 10 mg/kg/day, the only dose tested, in pigtail monkeys (about 1/20, 1/4, and 1/2 and 4 times the human dose, respectively, on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Although experience with humans administered VESANOID is extremely limited, increased spontaneous abortions and major human fetal abnormalities related to the use of other retinoids have been documented in humans. Reported defects include abnormalities of the CNS, musculoskeletal system, external ear, eye, thymus and great vessels; and facial dysmorphia, cleft palate, and parathyroid hormone deficiency. Some of these abnormalities were fatal. Cases of IQ scores less than 85, with or without obvious CNS abnormalities, have also been reported. All fetuses exposed during pregnancy can be affected and at the present time there is no antepartum means of determining which fetuses are and are not affected.

Effective contraception must be used by all females during VESANOID therapy and for 1 month following discontinuation of therapy. Contraception must be used even when there is a history of infertility or menopause, unless a hysterectomy has been performed. Whenever contraception is required, it is recommended that two reliable forms of contraception be used simultaneously, unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing or terminating the pregnancy.

Patients Without the t(15;17) Translocation: Initiation of therapy with VESANOID may be based on the morphological diagnosis of acute promyelocytic leukemia. Confirmation of the diagnosis of APL should be sought by detection of the t(15;17) genetic marker by cytogenetic studies. If these are negative, PML/RARα fusion should be sought using molecular diagnostic techniques. The response rate of other AML subtypes to VESANOID has not been demonstrated; therefore, patients who lack the genetic marker should be considered for alternative treatment.

Retinoic Acid-APL (RA-APL) Syndrome: In up to 25% of patients with APL treated with VESANOID, a syndrome occurs which can be fatal (see boxed WARNINGS and ADVERSE REACTIONS).

Leukocytosis at Presentation and Rapidly Evolving Leukocytosis During VESANOID Treatment: (see boxed WARNINGS).

Pseudotumor Cerebri: Retinoids, including VESANOID, have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in pediatric patients. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be evaluated for pseudotumor cerebri, and, if present, appropriate care should be instituted in concert with neurological assessment.

Lipids: Up to 60% of patients experienced hypercholesterolemia and/or hypertriglyceridemia, which were reversible upon completion of treatment. The clinical consequences of temporary elevation of triglycerides and cholesterol are unknown, but venous thrombosis and myocardial infarction have been reported in patients who ordinarily are at low risk for such complications.

Elevated Liver Function Test Results: Elevated liver function test results occur in 50% to 60% of patients during treatment. Liver function test results should be carefully monitored during treatment and consideration be given to a temporary withdrawal of VESANOID if test results reach >5 times the upper limit of normal values. However, the majority of these abnormalities resolve without interruption of VESANOID or after completion of treatment.

PRECAUTIONS: *General:* VESANOID has potentially significant toxic side effects in APL patients. Patients undergoing therapy should be closely observed for signs of respiratory compromise and/or leukocytosis (see boxed WARNINGS). Supportive care appropriate for APL patients; eg, prophylaxis for bleeding, prompt therapy for infection, should be maintained during therapy with VESANOID.

Laboratory Tests: The patient's hematologic profile, coagulation profile, liver function test results, and triglyceride and cholesterol levels should be monitored frequently.

Drug Interactions: Limited clinical data on potential drug interactions are available. As VESANOID is metabolized by the hepatic P450 system, there is a potential for alteration of pharmacokinetics parameters in patients administered concomitant medications that are also inducers or inhibitors of this system. Medications that generally induce hepatic P450 enzymes include rifampicin, glucocorticoids, phenobarbital and pentobarbital. Medications that generally inhibit hepatic P450 enzymes include ketoconazole, cimetidine, erythromycin, verapamil, diltiazem and cyclosporin. To date there are no data to suggest that co-use with these medications increases or decreases either efficacy or toxicity of VESANOID.

Effect of Food: No data on the effect of food on the absorption of VESANOID are available. The absorption of retinoids as a class has been shown to be enhanced when taken together with food.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term carcinogenicity studies with tretinoin have been conducted. In short-term carcinogenicity studies, tretinoin at a dose of 30 mg/kg/day (about 2 times the human dose on a mg/m² basis) was shown to increase the rate of diethylnitrosamine (DEN)-induced mouse liver adenomas and carcinomas. Tretinoin was negative when tested in the Ames and Chinese hamster V79 cell HGPRT assays for mutagenicity. A twofold increase in the sister chromatid exchange (SCE) has been demonstrated in human diploid fibroblasts, but other chromosome aberration assays, including an in vitro assay in human peripheral lymphocytes and an in vivo mouse micronucleus assay, did not show a clastogenic or aneuploidogenic effect. Adverse effects on fertility and reproductive performance were not observed in studies conducted in rats at doses up to 5 mg/kg/day (about 2/3 the human dose on a mg/m² basis). In a 6-week toxicology study in dogs, minimal to marked testicular degeneration, with increased numbers of immature spermatozoa, were observed at 10 mg/kg/day (about 4 times the equivalent human dose in mg/m²).

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from VESANOID in nursing infants, mothers should discontinue nursing prior to taking this drug.

Pediatric Use: There are limited clinical data on the pediatric use of VESANOID. Of 15 pediatric patients (age range: 1 to 16 years) treated with VESANOID, the incidence of complete remission was 67%. Safety and effectiveness in pediatric patients below the age of 1 year have not been established. Some pediatric patients experience severe headache and pseudotumor cerebri, requiring analgesic treatment and lumbar puncture for relief. Increased caution is recommended in the treatment of pediatric patients. Dose reduction may be considered for pediatric patients experiencing serious and/or intolerable toxicity; however, the efficacy and safety of VESANOID at doses lower than 45 mg/m²/day have not been evaluated in the pediatric population.

Geriatric Use: Of the total number of subjects in clinical studies of VESANOID, 21.4% were 60 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Virtually all patients experience some drug related toxicity, especially headache, fever, weakness, and fatigue. These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy. Some of the adverse events are common in patients with APL, including hemorrhage, infections, gastrointestinal hemorrhage, disseminated intravascular coagulation, pneumonia, septicemia, and cerebral hemorrhage. The following describes the adverse events, regardless of drug relationship, that were observed in patients treated with VESANOID.

Typical Retinoid Toxicity: The most frequently reported adverse events were similar to those described in patients taking high doses of vitamin A and included headache (86%), fever (83%), skin/mucous membrane dryness (77%), bone pain (77%), nausea/vomiting (57%), rash (54%), mucositis (26%), pruritus (20%), increased sweating (20%), visual disturbances (17%), ocular disorders (17%), alopecia (14%), skin changes (14%), changed visual acuity (6%), bone inflammation (3%), visual field defects (3%).

RA-APL Syndrome: APL patients treated with VESANOID have experienced a syndrome characterized by fever, dyspnea, weight gain, radiographic pulmonary infiltrates and pleural or pericardial effusions. This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension and has been observed with or without concomitant leukocytosis. Some patients have expired due to progressive hypoxemia and multiorgan failure. The syndrome generally occurs during the first month of treatment, with some cases reported following the first dose of VESANOID. The management of the syndrome has not been defined rigorously, but high-dose steroids given at the first signs of the syndrome appear to reduce morbidity and mortality. Treatment with dexamethasone, 10 mg intravenously administered every 12 hours for 3 days or until resolution of symptoms, should be initiated without delay at the first suspicion of symptoms (one or more of the following: fever, dyspnea, weight gain, abnormal chest auscultatory findings or radiographic abnormalities). Sixty percent or more of patients treated with VESANOID may require high-dose steroids because of these symptoms. The majority of patients do not require termination of VESANOID therapy during treatment of the syndrome.

Body as a Whole: General disorders related to VESANOID administration and/or associated with APL included malaise (66%), shivering (63%), hemorrhage (60%), infections (58%), peripheral edema (52%), pain (37%), chest discomfort (32%), edema (29%), disseminated intravascular coagulation (26%), weight increase (23%), injection site reactions (17%), anorexia (17%), weight decrease (17%), myalgia (14%), flank pain (9%), cellulitis (8%), face edema (6%), fluid imbalance (6%), pallor (6%), lymph disorders (6%), acidosis (3%), hypothermia (3%), ascites (3%).

Respiratory System Disorders: Respiratory system disorders were commonly reported in APL patients administered VESANOID. The majority of these events are symptoms of the RA-APL syndrome (see boxed WARNINGS). Respiratory system adverse events included upper respiratory tract disorders (63%), dyspnea (60%), respiratory insufficiency (26%), pleural effusion (20%), pneumonia (14%), rales (14%), expiratory wheezing (14%), lower respiratory tract disorders (9%), pulmonary infiltration (6%), bronchial asthma (3%), pulmonary edema (3%), larynx edema (3%), unspecified pulmonary disease (3%).

Ear Disorders: Ear disorders were consistently reported, with earache or feeling of fullness in the ears reported by 23% of the patients. Hearing loss and other unspecified auricular disorders were observed in 6% of patients, with infrequent (<1%) reports of irreversible hearing loss.

Gastrointestinal Disorders: GI disorders included GI hemorrhage (34%), abdominal pain (31%), other gastrointestinal disorders (26%), diarrhea (23%), constipation (17%), dyspepsia (14%), abdominal distention (11%), hepatosplenomegaly (9%), hepatitis (3%), ulcer (3%), unspecified liver disorder (3%).

Cardiovascular and Heart Rate and Rhythm Disorders: Arrhythmias (23%), flushing (23%), hypotension (14%), hypertension (11%), phlebitis (11%), cardiac failure (6%) and for 3% of patients: cardiac arrest, myocardial infarction, enlarged heart, heart murmur, tachycardia, stroke, myocarditis, pericarditis, pulmonary hypertension, secondary cardiomyopathy.

Central and Peripheral Nervous System Disorders and Psychiatric: Dizziness (20%), paresthesias (17%), anxiety (17%), insomnia (14%), depression (14%), confusion (11%), cerebral hemorrhage (9%), intracranial hypertension (9%), agitation (9%), hallucination (6%) and for 3% of patients: abnormal gait, agnosia, aphasia, asterixis, cerebellar edema, cerebellar disorders, convulsions, coma, CNS depression, dysarthria, encephalopathy, facial

VESANOID® (tretinoin)

paralysis, hemiplegia, hyporeflexia, hypotaxia, no light reflex, neurologic reaction, spinal cord disorder, tremor, leg weakness, unconsciousness, dementia, forgetfulness, somnolence, slow speech.

Urinary System Disorders: Renal insufficiency (11%), dysuria (9%), acute renal failure (3%), micturition frequency (3%), renal tubular necrosis (3%), enlarged prostate (3%).

Miscellaneous Adverse Events: Isolated cases of erythema nodosum, basophilia and hyperhistaminemia, Sweet's syndrome, organomegaly, hypercalcemia, pancreatitis and myositis have been reported.

OVERDOSAGE: There has been no experience with acute overdosage in humans. The maximal tolerated dose in patients with myelodysplastic syndrome or solid tumors was 195 mg/m²/day. The maximal tolerated dose in pediatric patients was lower at 60 mg/m²/day. Overdosage with other retinoids has been associated with transient headache, facial flushing, cheilosis, abdominal pain, dizziness and ataxia. These symptoms have quickly resolved without apparent residual effects.

DOSAGE AND ADMINISTRATION: The recommended dose is 45 mg/m²/day administered as two evenly divided doses until complete remission is documented. Therapy should be discontinued 30 days after achievement of complete remission or after 90 days of treatment, whichever occurs first.

If after initiation of treatment of VESANOID the presence of the t(15;17) translocation is not confirmed by cytogenetics and/or by polymerase chain reaction studies and the patient has not responded to VESANOID, alternative therapy appropriate for acute myelogenous leukemia should be considered.

VESANOID is for the induction of remission only. Optimal consolidation or maintenance regimens have not been determined. All patients should, therefore, receive a standard consolidation and/or maintenance chemotherapy regimen for APL after induction therapy with VESANOID, unless otherwise contraindicated.

HOW SUPPLIED: VESANOID is supplied as 10 mg capsules, two-tone (lengthwise), orange-yellow and reddish-brown and imprinted VESANOID 10 ROCHE. Supplied in high-density polyethylene, opaque Prescription Pak Bottles of 100 capsules with child-resistant closure (NDC 0004-0250-01).

Store at 15° to 30°C (59° to 86°F). Protect from light.

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

27897174-0500

Revised: May 2000
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-438/S-001

Administrative Documents

DIV File

CSO NDA LABELING REVIEW OF PACKAGE INSERT JUN 27 2000

NDA: 20-438

DATE OF SUBMISSION: FA for SLR-001 Geriatric / 8-18-99

DATE OF REVIEW: June 27, 2000

DRUG: Vesanoid (tretinoin) Capsules

SPONSOR: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

This submission provides the final printed labeling for the addition of a geriatric subsection.

I have reviewed the approved draft labeling, comparing it with the final printed labeling and have found it acceptable but noted that in the section CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions, the comma after "*CYP*" should be removed at the next printing. The sentence should read as follows:

> "The precise cytochrome P450 enzymes involved in these interactions have not been specified; *CYP* 3A4, 2C8 and 2E have been implicated in various preliminary reports."

/S/ 6-27-00
Maureen A. Pelosi
Project Manager

/S/ 6.27-00
Dotti Pease
Supervisor, Project Management

CC: Original NDA 20-438 SLR-001 (FA)
HFD-150/Div File
/Hirschfeld, Pelosi, Pease

Div File

FEB 2 2000

Original

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 20-438

DATE OF SUBMISSION: SLR-001 Geriatric / 8-18-99

DATE OF REVIEW: September 9, 1999

DRUG: Vesanoid (tretinoin) Capsules

SPONSOR: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

This submission provides for the addition of a geriatric subsection. Approximately 21% of the patients in the original clinical trials qualified as geriatric patients (48 of 224). No age related effects were observed. The sponsor believes that although they do not have the recommended sample size >100 geriatric patients, the percent is significant enough to submit a geriatric subsection labeling proposal. The Medical Officer should decide if this rationale is acceptable.

I have reviewed the draft labeling, comparing it with the approved labeling and have identified a few clinical pharmacology changes in addition to the geriatric subsection. These are changes which were requested in our March 8, 1996 letter accepting the FPL. Clinical Pharmacology should concur with these changes.

1. CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions on page 4: "CYP system" has been changed to "cytochrome P450" and is acceptable. However, the comma after "*CYP*" should be removed. In the Metabolism subsection, in the second sentence, "CYP" has been removed and is acceptable.

2. PRECAUTIONS, Drug Interactions on the bottom of page 6 and top of page 7: "CYP" has been changed "P450" as requested. However, in addition, we would like to insert "cytochrome" before the three uses of "P450".

/S/ / 9-9-99
Maureen A. Pelosi
Project Manager

Concur: /S/ 02/0/00
Atik Rahman, Ph.D.
OCBP, Team Leader

/S/ 2-2-00
Dotti Pease
Supervisor, Project Management

Concur/Not Concur: /S/ 12/3/99
Steven Hirschfeld, M.D., Ph.D.
Medical Officer

CC: Original NDA 20-438 SLR-001
HFD-150/Div File
/Hirschfeld,Pelosi, Rahman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-438/S-001

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

AUG 24 1999

Attention: Lynn DeVenezia-Tobias
Program Manger

Dear Ms. DeVenezia-Tobias:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Vesanoid (tretinoin) Capsules

NDA Number: 20-438

Supplement Number: S-001

Date of Supplement: August 18, 1999

Date of Receipt: August 19, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 18, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

/S/ 8/24/99

for

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-438/S-001
HFD-150/Div. Files
HFD-150/CSO/M. Pelosi

filename: C:\WPWIN61\TEMPLATE\FDA\20-438S0.WPD

SUPPLEMENT ACKNOWLEDGMENT