CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-746

FINAL PRINTED LABELING

RHINOCORT® AQUA™ (budesonide) NASAL SPRAY 32 mcg and 64 mcg

Unannotated Proposed Package Insert

NDA 20-746

APPEARS THIS WAY
ON ORIGINAL

RHINOCORT® AQUA™ (budesonide) NASAL SPRAY 32 mcg and 64 mcg

For Intranasal Inhalation Only

DESCRIPTION

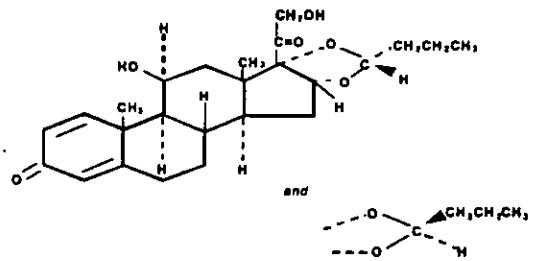
Budesonide, the active ingredient of RHINOCORT AQUA Nasal Spray, is an anti-inflammatory synthetic corticosteroid.

It is designated chemically as [(RS)-11-beta, 16-alpha, 17, 21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16, 17-acetal with butyraldehyde].

Budesonide is provided as the mixture of two epimers (22R and 22S).

The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Its structural formula is:



Budesonide is a white to off-white, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

Its partition coefficient between octanol and water at pH 5 is 1.6×10^3.

RHINOCORT AQUA is an unscented, metered-dose, manual-pump spray formulation containing a micronized suspension of budesonide in an aqueous medium. Microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate and purified water are contained in this medium; hydrochloric acid is added to adjust the pH to a target of 4.5.

RHINOCORT AQUA Nasal Spray is available in two dose strengths which deliver 32 mcg and 64 mcg, respectively, of budesonide per spray.

Each bottle of RHINOCORT AQUA Nasal Spray 32 mcg contains 60 or 120 metered sprays after initial priming.

Each bottle of RHINOCORT AQUA Nasal Spray 64 mcg contains 120 metered sprays after initial priming.

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating eight times. If used daily, the pump does not need to be reprimed. If not used for two consecutive

days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with two sprays or until a fine spray appears.

CLINICAL PHARMACOLOGY

Budesonide is a synthetic corticosteroid having potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in-vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. In glucocorticoid receptor affinity studies, the 22R form was twice as active as the 22S epimer.

The precise mechanism of corticosteroid actions in seasonal and perennial allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (*e.g.* mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (*e.g.* histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic mediated inflammation.

Corticosteroids affect the delayed (6 hour) response to an allergen challenge more than the histamine-associated immediate response (20 minute). The clinical significance of these findings is unknown.

Pharmacokinetics: The pharmacokinetics of budesonide have been studied following nasal, oral and intravenous administration. Budesonide is relatively well absorbed after both inhalation and oral administration, and is rapidly metabolized into metabolites with low corticosteroid potency. The clinical activity of RHINOCORT AQUA Nasal Spray is therefore believed to be due to the parent drug, budesonide. *In-vitro* studies indicate that the two epimeric forms of budesonide do not interconvert.

Absorption: Following intranasal administration of RHINOCORT AQUA, the mean peak plasma concentration occurs at approximately 0.7 hours. Compared to an intravenous dose, approximately 34% of the delivered intranasal dose reaches the systemic circulation, most of which is absorbed through the nasal mucosa. While budesonide is well absorbed from the GI tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first pass metabolism in the liver.

Distribution: Budesonide has a volume of distribution of approximately 2-3 L/kg. The volume of distribution for the 22R epimer is almost twice that of the 22S epimer. Protein binding of budesonide in vitro is constant (85 -90%) over a concentration range (1-100 nmol/L) which exceeded that achieved after administration of recommended doses. Budesonide shows little to no binding to glucocorticosteroid binding globulin. It rapidly equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via cytochrome P450 3A isoenzyme-catalyzed biotransformation. Known metabolic inhibitors of cytochrome P450 3A (*e.g.*, ketoconazole), or significant hepatic impairment, may increase the systemic exposure of unmetabolized budesonide (see WARNINGS and PRECAUTIONS). *In-vitro* studies on the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound budesonide. *In-vitro* studies have evaluated sites of metabolism and showed negligible metabolism in skin, lung, and serum. No qualitative difference

between the *in-vitro* and *in-vivo* metabolic patterns could be detected.

Elimination: Budesonide is excreted in the urine and feces in the form of metabolites. After intranasal administration of a radio labeled dose, 2/3 of the radioactivity was found in the urine and the remainder in the feces. The main metabolites of budesonide in the 0-24 hour urine sample following IV administration are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine was identified as conjugates.

The 22R form was preferentially cleared with clearance value of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was similar for both epimers and it appeared to be independent of dose.

Special Populations
Geriatric: No specific pharmacokinetic study has been undertaken in subjects >65 years of age.

Pediatric: After administration of RHINOCORT AQUA Nasal Spray, the time to reach peak drug concentrations and plasma half-life were similar in children and in adults. Children had plasma concentrations approximately twice those observed in adults due primarily to differences in weight between children and adults.

Gender: No specific pharmacokinetic study has been conducted to evaluate the effect of gender on budesonide pharmacokinetics. However, following administration of 400 mcg RHINOCORT AQUA Nasal Spray to 7 male and 8 female volunteers in a pharmacokinetic study, no major gender differences in the pharmacokinetic parameters were found.

Race: No specific study has been undertaken to evaluate the effect of race on budesonide pharmacokinetics.

Renal Insufficiency: The pharmacokinetics of budesonide have not been investigated in patients with renal insufficiency.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of orally administered budesonide were affected by compromised liver function as evidenced by a doubled systemic availability. The relevance of this finding to intranasally administered budesonide has not been established.

Pharmacodynamics: A 3-week clinical study in seasonal rhinitis, comparing RHINOCORT Nasal Inhaler, orally ingested budesonide, and placebo in 98 patients with allergic rhinitis due to birch pollen, demonstrated that the therapeutic effect of RHINOCORT Nasal Inhaler can be attributed to the topical effects of budesonide.

The effects of RHINOCORT AQUA Nasal Spray on adrenal function have been evaluated in several clinical trials. In a four-week clinical trial, 61 adult patients who received 256 mcg daily of RHINOCORT AQUA Nasal Spray demonstrated no significant differences from patients receiving placebo in plasma cortisol levels measured before and 60 minutes after 0.25 mg intramuscular cosyntropin. There were no consistent differences in 24-hour urinary cortisol measurements in patients receiving up to 400 mcg daily. Similar results were seen in a study of 150 children and adolescents aged 6 to 17 with perennial rhinitis who were treated with 256 mcg daily for up to twelve

months.

After treatment with the recommended maximal daily dose of RHINOCORT AQUA (256 mcg) for seven days, there was a small, but statistically significant decrease in the area under the plasma cortisol-time curve over 24 hours (AUC_{0-24h}) in healthy adult volunteers.

A dose-related suppression of 24-hour urinary cortisol excretion was observed after administration of RHINOCORT AQUA doses ranging from 100-800 mcg daily for up to four days in 78 healthy adult volunteers. The clinical relevance of these results is unknown.

Clinical Trials: The therapeutic efficacy of RHINOCORT AQUA Nasal Spray has been evaluated in placebo-controlled clinical trials of seasonal and perennial allergic rhinitis of 3-6 weeks duration.

The number of patients treated with budesonide in these studies was 90 males and 51 females aged 6-12 years and 691 males and 694 females 12 years and above. The patients were predominantly Caucasian.

Overall, the results of these clinical trials showed that RHINOCORT AQUA Nasal Spray administered once daily provides statistically significant reduction in the severity of nasal symptoms of seasonal and perennial allergic rhinitis including runny nose, sneezing, and nasal congestion.

In some studies, improvement versus placebo has been shown to occur within 24 hours of initiating treatment with RHINOCORT AQUA Nasal Spray. Maximum benefit is generally not achieved until 2 weeks after initiation of treatment.

INDICATIONS AND USAGE

RHINOCORT AQUA Nasal Spray is indicated for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients in this preparation contraindicates the use of RHINOCORT AQUA Nasal Spray.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of corticosteroid withdrawal, *e.g.* joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on immunosuppressant doses of corticosteroids. In such children or adults, who have not had these diseases, particular care should be taken to avoid

exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General: Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use).

Rarely, immediate and/or delayed hypersensitivity reactions may occur after the intranasal administration of budesonide. Rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including budesonide.

Although systemic effects have been minimal with recommended doses of RHINOCORT AQUA Nasal Spray, any such effect is dose dependent. Therefore, larger than recommended doses of RHINOCORT AQUA Nasal Spray should be avoided and the minimal effective dose for the patient should be used (see DOSAGE and ADMINISTRATION). When used at larger doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of RHINOCORT AQUA Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with budesonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local or systemic therapy and discontinuation of treatment with RHINOCORT AQUA Nasal Spray. Patients using RHINOCORT AQUA Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

RHINOCORT AQUA Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection, untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Hepatic dysfunction influences the pharmacokinetics of budesonide, similar to the effect on other corticosteroids, with a reduced elimination rate and increased systemic availability (see CLINICAL PHARMACOLOGY, Special Populations).

Information for Patients: Patients being treated with RHINOCORT AQUA Nasal Spray should receive the following information and instructions. Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

Patients should use RHINOCORT AQUA Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE and ADMINISTRATION).

An improvement in nasal symptoms may be seen within the first 24 hours after initiation of treatment. Maximum benefit is generally not achieved until 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after two weeks, or if the condition worsens. Patients who experience recurrent episodes of epistaxis (nosebleeds) or nasal septum discomfort while taking this medication should contact their physician. For proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully.

It is important to shake the bottle well before each use. The RHINOCORT AQUA Nasal Spray 32 mcg bottle should be discarded after 60 or 120 sprays after initial priming and the RHINOCORT AQUA Nasal Spray 64 mcg bottle should be discarded after 120 sprays, after initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Do not transfer any remaining suspension to another bottle.

Drug Interactions: The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 3A (CYP3A). After oral administration of ketoconazole, a potent inhibitor of cytochrome P450 3A, the mean plasma concentration of orally administered budesonide increased by more than seven fold. Concomitant administration of other known inhibitors of CYP3A (*e.g.* itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide (see WARNINGS, PRECAUTIONS, General).

Omeprazole, an inhibitor of cytochrome P450 2C19, did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of cytochrome P450 1A2, caused a slight decrease in budesonide clearance and corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in the male rats receiving an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equal to and two times the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis). However, in male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames, *salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hematocyte culture.

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

Pregnancy: Teratogenic Effects: Pregnancy Category C: Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits and 500 mcg/kg in rats (approximately 2 and 16 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. RHINOCORT AQUA Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when RHINOCORT AQUA Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients below 6 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, should be monitored routinely (*e.g.*, via stadiometry). The

potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

Geriatric Use: Of the 2,461 patients in clinical studies of RHINOCORT AQUA Nasal Spray, 5% were 60 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, except for an adverse event reporting frequency of epistaxis which increased with age. Further, other reported clinical experience has not identified any other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The incidence of common adverse reactions is based upon two U.S. and five non-U.S. controlled clinical trials in 1526 patients [110 females and 239 males less than 18 years of age, and 635 females and 542 males 18 years of age and older] treated with RHINOCORT AQUA Nasal Spray at doses up to 400 mcg once daily for 3-6 weeks. The table below describes adverse events occurring at an incidence of 2% or greater and more common among RHINOCORT AQUA Nasal Spray-treated patients than in placebo-treated patients in controlled clinical trials. The overall incidence of adverse events was similar between RHINOCORT AQUA and Placebo.

Adverse Event	RHINOCORT AQUA	Placebo Vehicle
Epistaxis	8%	5%
Pharyngitis	4%	3%
Bronchospasm	2%	1%
Coughing	2%	<1%
Nasal Irritation	2%	<1%

A similar adverse event profile was observed in the subgroup of pediatric patients 6 to 12 years of age.

Two to three percent (2-3%) of patients in clinical trials discontinued because of adverse events. Systemic corticosteroid side-effects were not reported during controlled clinical studies with RHINOCORT AQUA Nasal Spray.

If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, *i.e.*, Cushing's Syndrome, could occur.

Rare adverse events reported from post-marketing experience include: nasal septum perforation, pharynx disorders (throat irritation, throat pain, swollen throat, burning throat, and itchy throat), angioedema, anosmia, and palpitations.

Cases of growth suppression have been reported for intranasal corticosteroids including RHINOCORT AQUA Nasal Spray (see PRECAUTIONS, Pediatric Use).

OVERDOSAGE

Acute overdosage with this dosage form is unlikely since one 60 spray bottle of RHINOCORT AQUA Nasal Spray 32 mcg only contains approximately 3.2 mg of budesonide, one 120 spray bottle of RHINOCORT AQUA Nasal Spray 32 mcg contains approximately 5.4 mg of budesonide, and one 120 spray bottle of RHINOCORT AQUA Nasal Spray 64 mcg only contains approximately 10.8 mg of budesonide. Chronic overdosage may result in signs/symptoms of hypercorticism (see WARNINGS and PRECAUTIONS).

DOSAGE AND ADMINISTRATION

The recommended starting dose for adults and children 6 years of age and older is 64 mcg per day administered as one spray per nostril of RHINOCORT AQUA 32 mcg Nasal Spray once daily. The maximum recommended dose for adults (12 years of age and older) is 256 mcg per day administered as four sprays per nostril once daily of RHINOCORT AQUA 32 mcg Nasal Spray, or as two sprays per nostril once daily of RHINOCORT AQUA 64 mcg Nasal Spray, and the maximum recommended dose for pediatrics (<12 years of age) is 128 mcg per day administered as two sprays per nostril once daily of RHINOCORT AQUA 32 mcg Nasal Spray or one spray per nostril once daily of RHINOCORT AQUA Nasal Spray (see HOW SUPPLIED).

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating eight times. If used daily, the pump does not need to be reprimed. If not used for two consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with two sprays or until a fine spray appears.

Individualization of Dosage: It is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. In adults and children 6 years of age and older, the recommended starting dose is 64 mcg daily administered as one spray per nostril of RHINOCORT AQUA Nasal Spray 32 mcg, once-daily. Some patients who do not achieve symptom control at the recommended starting dose may benefit from an increased dose. The maximum daily dose is 256 mcg for adults and 128 mcg for pediatric patients (<12 years of age). When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose may be effective in maintaining control of the allergic rhinitis symptoms in patients who were initially controlled on higher doses.

An improvement in symptoms may be seen in some patients within the first 24 hours after initiating treatment. Maximum benefit is generally not achieved until 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of RHINOCORT AQUA 32 mcg Nasal Spray or RHINOCORT AQUA 64 mcg Nasal Spray.

HOW SUPPLIED

RHINOCORT AQUA Nasal Spray is available in two strengths (32 mcg and 64 mcg) in a 10 mL green coated glass bottle with a metered-dose pump spray with a green protection cap and patient instructions for use. Each spray delivers 32 mcg or 64 mcg of budesonide to the patient. RHINOCORT AQUA Nasal Spray 32 mcg dose is available in bottles containing 60 or 120 metered sprays, after initial priming. RHINOCORT AQUA Nasal Spray 64 mcg dose is available in bottles

containing 120 metered sprays, after initial priming.

NDC 0186-1070-06
RHINOCORT AQUA Nasal Spray
32 mcg, 60 metered sprays.

NDC 0186-1070-08
RHINOCORT AQUA Nasal Spray
32 mcg, 120 metered sprays.

NDC 0186-0171-08
RHINOCORT AQUA Nasal Spray
64 mcg, 120 metered sprays.

Rx only.

RHINOCORT AQUA Nasal Spray should be stored at controlled room temperature, 20 to 25°C (68 to 77°F) with the valve up. Do not freeze. Protect from light. **Shake gently before use.** Do not spray in eyes.

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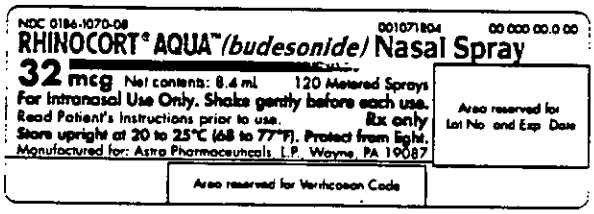

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Astra Pharmaceuticals

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RHINOCORT® AQUA™ *(budesonide)*
Nasal Spray 32 mcg

Net contents: 8.4 mL
120 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

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RHINOCORT® AQUA™ *(budesonide)*
Nasal Spray 32 mcg

Net contents: 8.4 mL
120 Metered Sprays

After initial priming (eight actuations), each 51 mg spray delivered by the nasal applicator contains 32 mcg of budesonide. Refer to package insert and Patient's Instructions for full priming and cleaning information.

Contents: Each unit contains budesonide in a suspension of microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, HCl to pH 4.5 and purified water.

NDC 0186-1070-08

RHINOCORT® AQUA™ *(budesonide)*
Nasal Spray 32 mcg

Net contents: 8.4 mL
120 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA

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RHINOCORT® AQUA™ *(budesonide)*
Nasal Spray 32 mcg

Net contents: 8.4 mL
120 Metered Sprays

Attention Health Care Provider: Consult the package insert for dosage and full prescribing information.

Attention Patient — Important: Read accompanying Patient's Instructions carefully prior to using. **Store upright at controlled room temperature, 20 to 25°C (68 to 77°F). Do not freeze. Protect from light.**

Shake gently before each use. Do not spray in eyes.

Keep out of reach of children. RHINOCORT AQUA is not recommended for children under 6 years of age.

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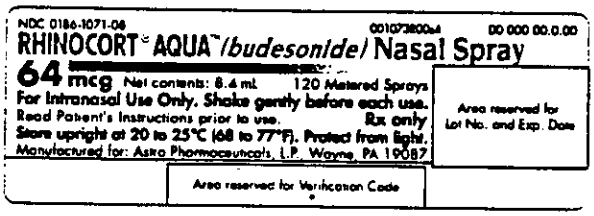

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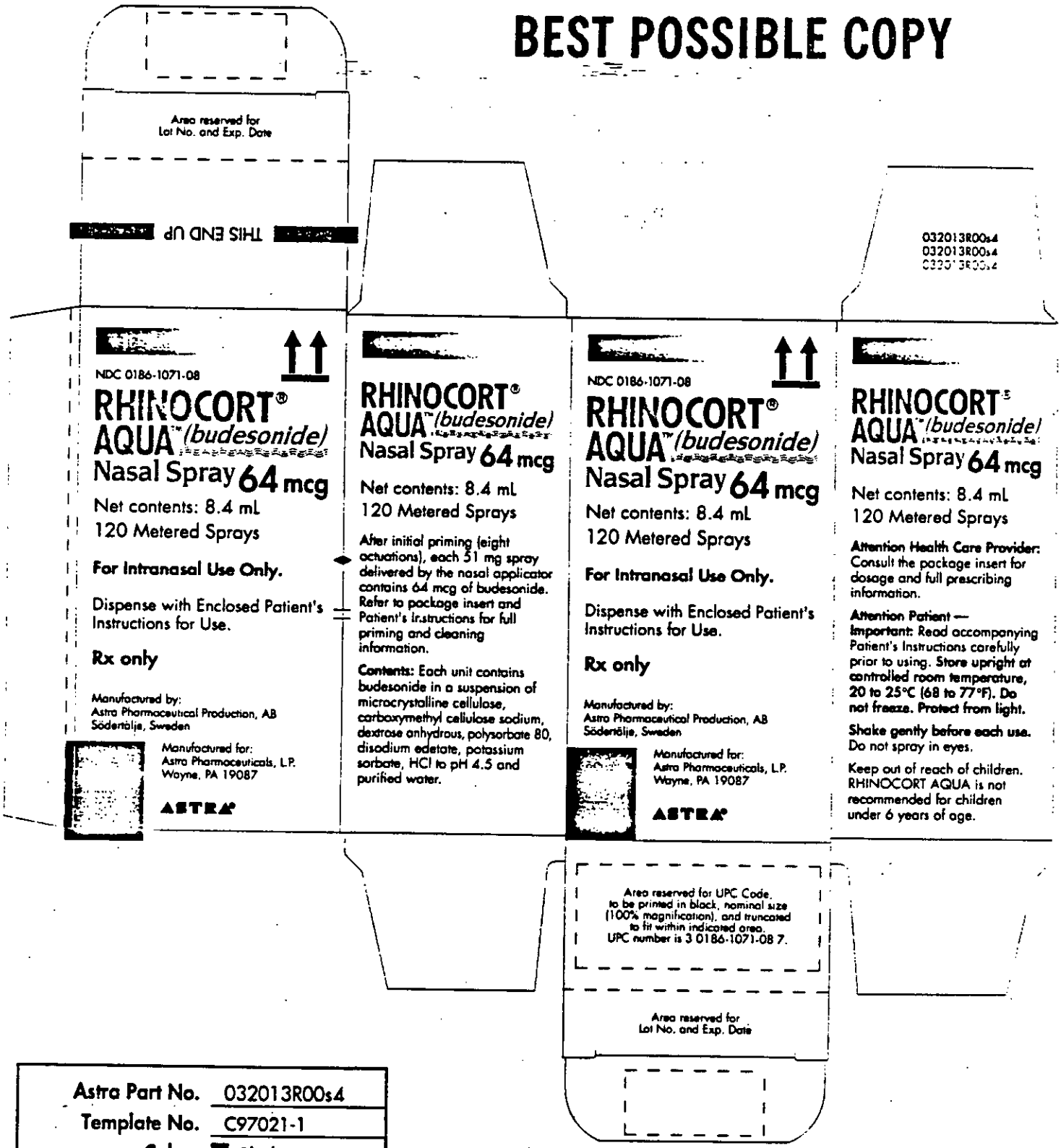

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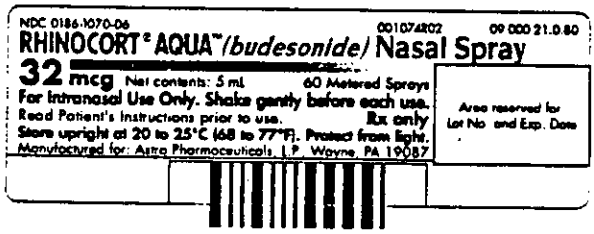

Astra Part No.	001074R02
Template No.	L98009
Colors	■ Black
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ASTRA
Astra Pharmaceuticals

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Area reserved for
Lot No. and Exp. Date

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032036R03
032036R03

NDC 0186-1070-06

RHINOCORT® AQUA™ (budesonide)

Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg
Net contents: 5 mL
60 Metered Sprays

After initial priming (eight actuations), each 51 mg spray delivered by the nasal applicator contains 32 mcg of budesonide. Refer to package insert and Patient's Instructions for full priming and cleaning information.

Contents: Each unit contains budesonide in a suspension of microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, HCl to pH 4.5 and purified water.

NDC 0186-1070-06

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg
Net contents: 5 mL
60 Metered Sprays

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Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg
Net contents: 5 mL
60 Metered Sprays

Attention Health Care Provider: Consult the package insert for dosage and full prescribing information.

Attention Patient — Important: Read accompanying Patient's Instructions carefully prior to using. **Store upright at controlled room temperature, 20 to 25°C (68 to 77°F). Do not freeze. Protect from light.**

Shake gently before each use. Do not spray in eyes.

Keep out of reach of children. RHINOCORT AQUA is not recommended for children under 6 years of age.

Area reserved for UPC Code, to be printed in black, nominal size (100% magnification), and truncated to fit within indicated area. UPC number is 3 0186-1070-06 6.

Area reserved for
Lot No. and Exp. Date

Astra Part No.	032036R03
Template No.	C97021-1
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	Full Varnish

ASTRA® Astra Pharmaceuticals

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Lot No. and Exp. Date

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032028R04
032028R04

NDC 0186-1070-66

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

PROFESSIONAL SAMPLE
NOT FOR RESALE

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

After initial priming (eight actuations), each 51 mg spray delivered by the nasal applicator contains 32 mcg of budesonide. Refer to package insert and Patient's Instructions for full priming and cleaning information.

Contents: Each unit contains budesonide in a suspension of microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, HCl to pH 4.5 and purified water.

NDC 0186-1070-66

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

PROFESSIONAL SAMPLE
NOT FOR RESALE

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

Attention Health Care Provider: Consult the package insert for dosage and full prescribing information.

Attention Patient — Important: Read accompanying Patient's Instructions carefully prior to using. **Store upright at controlled room temperature, 20 to 25°C (68 to 77°F). Do not freeze. Protect from light.**

Shake gently before each use. Do not spray in eyes.

Keep out of reach of children. RHINOCORT AQUA is not recommended for children under 6 years of age.

Area reserved for
Lot No. and Exp. Date

Astra Part No.	032028R04
Template No.	C97021-1
Colors	■ Black
	■ ☐ Blue
	Full Varnish

ASTRA
Astra Pharmaceuticals

APPEARS THIS WAY
ON ORIGINAL

/S/
SEP 27 1999

PROJECT MANAGER LABELING REVIEW

NDA:	20-746
REVIEW DATE:	September 27, 1999
DRUG:	Rhinocort Aqua (budesonide) Nasal Spray
SPONSOR:	AstraZeneca
PROJECT MANAGER:	Gretchen Trout
SUBMISSION:	September 24, 1999

The Division had requested that Astra resubmit, in one submission, the package insert (previously submitted on August 30, 1999), patient instruction leaflet (previously submitted on July 20, 1999), and the carton and container labels for the initial launch of the product (previously submitted on July 30, 1999). I compared the September 24, 1999, submission with the previous submissions and determined that they are identical.

/S/
Gretchen Trout
Project Manager

9/24/99
Date

cc:
Orig NDA # 20-746
HFD-570 Division File

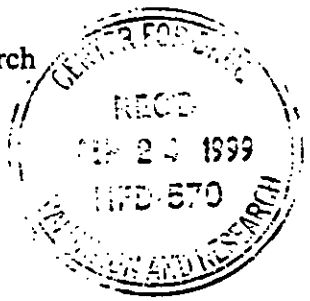
APPEARS THIS WAY
ON ORIGINAL

AstraZeneca

Eric Couture, Ph.D.
Director, Regulatory Liaison

September 24, 1999

Robert Meyer, M.D., Director
Division of Pulmonary Drug Products
HFD-570 Room 10-B03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. Meyer:

NDA 20-746
Rhinocort® Aqua™ (Budesonide) Nasal Spray
Labeling Submission: Response to FDA Request for Information

Please refer to our July 29, 1996 New Drug Application for Rhinocort Aqua (Budesonide) Nasal Spray, 32 mcg and 64 mcg, to our teleconferences on July 13 and July 26, 1999 to discuss issues related to the label and carton, to our submissions to FDA dated July 20, July 30, and August 30, 1999, and to our conversations with Ms. Gretchen Trout on September 22 and September 23, 1999.

As requested, attached are copies of the following items:

- Annotated and Unannotated Package Inserts for Rhinocort Aqua (Budesonide) Nasal Inhaler 32 and 64 mcg (previously submitted on August 30, 1999).
- Patient Instruction leaflets for 32 and 64 mcg presentations (previously submitted on July 20, 1999).
- Cartons and "current" bottle labels for 32 mcg/60 spray presentation to be used for initial launch quantities (previously submitted on July 30, 1999).
- Cartons and "new" bottle labels for all other 32 and 64 mcg presentations (previously submitted on July 30, 1999).

No changes have been made to these items since their previous submission to the Agency.

AstraZeneca LP
725 Chesterbrook Blvd Wayne PA 19087-5677

Tel 610 695 1000
www.astrazeneca-us.com

Please direct any questions or comments to me at (610) 695-1263 or, in my absence, to Robert Monaghan, Senior Regulatory Project Manager at (610) 695-4227.

Sincerely yours,

Eric Couture, Ph.D.
Director, Regulatory Liaison

Enclosure
cc: Gretchen Trout, Regulatory Project Manager

Sent via courier

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
AstraZeneca LP

DATE OF SUBMISSION
09/24/99

TELEPHONE NO. *(Include Area Code)*
610-695-1263

FACSIMILE (FAX) Number *(Include Area Code)*
610-722-7784

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-746

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Budesonide

PROPRIETARY NAME *(trade name)* IF ANY Rhinocort® Aqua™ Nasal Spray

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Tetrahydroxypregna-1, 4-diene-3, 20-dionecyclic 16, 17-acetal with butyraldehyde

CODE NAME *(If any)* S-1320

DOSAGE FORM: Suspension

STRENGTHS: 32ug and 64ug

ROUTE OF ADMINISTRATION: Nasal

(PROPOSED) INDICATION(S) FOR USE:
Management of symptoms of seasonal or perennial allergic rhinitis in adults and children (6 years or older)

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION General Correspondence - Response to FDA request for information

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to FDA Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
E. Couture	Eric Couture, Ph.D., Director, Regulatory Liaison	24 September 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
725 Chesterbrook Blvd. Wayne, PA 19087-5677	(610) 695-1263

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

TABLE OF CONTENTS

11 **Page(s) Redacted**

Draft

Labeling

Instructions for using your

RHINOCORT® AQUA™ *(budesonide)* Nasal Spray 32 mcg

60 Metered Sprays

IMPORTANT: Please read this leaflet carefully before you start to use RHINOCORT AQUA Nasal Spray. It provides a summary of information about your medicine. FOR FURTHER INFORMATION, ASK YOUR DOCTOR OR PHARMACIST.

WHAT YOU SHOULD KNOW ABOUT RHINOCORT AQUA NASAL SPRAY

Your doctor has prescribed RHINOCORT AQUA Nasal Spray, a medicine that can help treat your nasal symptoms due to perennial or seasonal allergic rhinitis. RHINOCORT AQUA Nasal Spray contains budesonide, a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. When you spray RHINOCORT AQUA Nasal Spray into your nose, it helps to relieve or prevent your nasal stuffiness, runny nose, and sneezing that are caused by the inflammation.

BEFORE USING YOUR RHINOCORT AQUA NASAL SPRAY

BEFORE STARTING TO TAKE THIS MEDICINE, TELL YOUR DOCTOR:

- If you are pregnant (or intending to become pregnant),
- If you are breast-feeding a baby,
- If you are allergic to budesonide or any other nasal inhaled corticosteroid.

In some circumstances, this medicine may not be suitable, and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicine you are taking.

USING YOUR RHINOCORT AQUA NASAL SPRAY

- Follow the instructions on the reverse side of this page. If you have any problems, tell your doctor or pharmacist.
- It is important that you use RHINOCORT AQUA Nasal Spray as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't or you are not sure how to use RHINOCORT AQUA Nasal Spray, ask your doctor or pharmacist.

DOSAGE

- Use as directed by your doctor.
- It is VERY IMPORTANT that you follow your doctor's instructions as to how many sprays to take and how often to use your RHINOCORT AQUA Nasal Spray.
- DO NOT take more doses or use RHINOCORT AQUA Nasal Spray more often than your doctor tells you.
- IT IS VERY IMPORTANT THAT YOU USE RHINOCORT AQUA NASAL SPRAY REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE, EVEN IF YOU ARE FEELING BETTER, unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE the dose.
- If you also have itchy, watery eyes, you should tell your doctor. He or she can prescribe additional medication to treat these symptoms.

STORING YOUR RHINOCORT AQUA NASAL SPRAY

- Keep the green protective cap on RHINOCORT AQUA Nasal Spray when not in use. (Please see Prior To Use on reverse side)
- Keep RHINOCORT AQUA Nasal Spray and all medications out of the reach of children.
- Keep RHINOCORT AQUA Nasal Spray in a dry place at controlled room temperature, 68 to 77°F (20 to 25°C). Do not freeze. Protect from light.
- Do not use RHINOCORT AQUA Nasal Spray after 60 sprays (does not include priming) or after the expiration date shown on the carton or bottle label.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medicine. If you have any questions, or are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

HOW TO USE YOUR RHINOCORT AQUA NASAL SPRAY

Read the complete instructions carefully and use only as directed.

Prior To Use:

Before using RHINOCORT AQUA Nasal Spray for the first time, the bottle must be primed. To do this:

1. Pull to remove the green protective cap off the nasal spray unit.
2. Shake the bottle gently for a few seconds before each use.
3. Hold the bottle firmly, as shown in Figure A, with your index and middle finger on either side of the spray tip and your thumb underneath the bottle.
4. Actuate the pump by QUICKLY and FIRMLY pressing down on the white collar while supporting the base of the bottle with your thumb.
5. Prior to initial use, shake the bottle gently. The pump must be primed by actuating 8 times. If used daily the pump does not need to be reprimed. If not used for 2 consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator using the cleaning steps listed below. Reprime with two sprays or until a fine spray appears.
6. Do not spray in eyes.

NOTE: Your RHINOCORT AQUA Nasal Spray has been filled with an excess to accommodate the priming activity. The correct amount of medication in each spray cannot be assured after the labelled number of sprays even though the container is not completely empty. Keep track of the number of sprays released from the container. Do not transfer any remaining RHINOCORT AQUA Nasal Spray to another bottle.

Instructions For Daily Use:

Follow these instructions for daily use of RHINOCORT AQUA Nasal Spray:

1. Gently blow your nose to clear your nostrils, if necessary.
2. Shake the bottle gently for a few seconds and remove the green protective cap.
3. Hold the bottle firmly with your index and middle finger on either side of the spray tip and your thumb underneath the bottle (Figure A).

Figure A

4. Insert the spray tip into your nostril (the tip should not reach far into your nose). Close the other nostril with a finger and lean your head slightly forward so the spray will aim toward the back of your nose (Figure B).

Figure B

5. For each spray, actuate the pump by QUICKLY and FIRMLY pressing down on the white collar while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril.
6. After spraying into your nostril, lean your head backward for a few seconds (Figure C).

Figure C

7. If a second spray is required in the same nostril, repeat steps 3 through 6.
8. Repeat steps 3 through 7 for your other nostril.
9. Avoid blowing your nose for 15 minutes after using RHINOCORT AQUA Nasal Spray.
10. Wipe the spray tip with a clean tissue (Figure D), and replace the green protective cap. Store the bottle in an upright position.

Figure D

CLEANING

Rinse the upper plastic parts regularly. To do this:

1. Remove the green protective cap and lift off the spray tip.
2. Wash only these plastic parts in warm water and rinse them in cold tap water.
3. Allow the plastic parts to air-dry completely before reassembling the nasal spray.
4. If the spray tip becomes blocked, it can be cleared by performing the above steps. **DO NOT TRY TO UNBLOCK THE NASAL APPLICATOR BY USING A PIN OR OTHER SHARP OBJECT.**

Manufactured for:
ASTRA
Astra Pharmaceuticals, L.P., Wayne, PA 19087
021790R00x3
Rev 9/99

021870R00x1

Instructions for using your

Rhinocort® Aqua™ *(budesonide)* Nasal Spray 32 mcg

120 Metered Sprays

IMPORTANT: Please read this leaflet carefully before you start to use Rhinocort Aqua Nasal Spray. It provides a summary of information about your medicine. FOR FURTHER INFORMATION, ASK YOUR DOCTOR OR PHARMACIST.

WHAT YOU SHOULD KNOW ABOUT RHINOCORT AQUA NASAL SPRAY

Your doctor has prescribed Rhinocort Aqua Nasal Spray, a medicine that can help treat your nasal symptoms due to perennial or seasonal allergic rhinitis. Rhinocort Aqua Nasal Spray contains budesonide, a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. When you spray Rhinocort Aqua Nasal Spray into your nose, it helps to relieve or prevent your nasal stuffiness, itching, and sneezing that are caused by the inflammation.

BEFORE USING YOUR RHINOCORT AQUA NASAL SPRAY

BEFORE STARTING TO TAKE THIS MEDICINE, TELL YOUR DOCTOR:

- if you are pregnant (or intending to become pregnant),
- if you are breast-feeding a baby,
- if you are allergic to budesonide or any other nasal inhaled corticosteroid.

In some circumstances, this medicine may not be suitable, and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicine you are taking.

USING YOUR RHINOCORT AQUA NASAL SPRAY

- Follow the instructions on the reverse side of this page. If you have any problems, tell your doctor or pharmacist.
- It is important that you use Rhinocort Aqua Nasal Spray as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't or you are not sure how to use Rhinocort Aqua Nasal Spray, ask your doctor or pharmacist.

DOSAGE

- Use as directed by your doctor.
- It is VERY IMPORTANT that you follow your doctor's instructions as to how many sprays to take and how often to use your Rhinocort Aqua Nasal Spray.
- DO NOT take more doses or use Rhinocort Aqua Nasal Spray more often than your doctor tells you.
- IT IS VERY IMPORTANT THAT YOU USE RHINOCORT AQUA NASAL SPRAY REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE, EVEN IF YOU ARE FEELING BETTER, unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE the dose.
- If you also have itchy, watery eyes, you should tell your doctor. He or she can prescribe additional medication to treat these symptoms.

STORING YOUR RHINOCORT AQUA NASAL SPRAY

- Keep the green protective cap on Rhinocort Aqua Nasal Spray when not in use. (Please see Prior To Use on reverse side)
- Keep Rhinocort Aqua Nasal Spray and all medications **out of the reach of children.**
- Keep Rhinocort Aqua Nasal Spray in a dry place at controlled room temperature, 68 to 77°F (20 to 25°C). Do not freeze. Protect from light.
- Do not use Rhinocort Aqua Nasal Spray after 120 sprays (does not include priming) or after the expiration date shown on the carton.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medicine. If you have any questions, or are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

HOW TO USE YOUR RHINOCORT AQUA NASAL SPRAY

Read the complete instructions carefully and use only as directed.

Prior To Use:

Before using Rhinocort Aqua Nasal Spray for the first time, the bottle must be primed. To do this:

1. Pull to remove the green protective cap off the nasal spray unit.
2. **Shake the bottle gently for a few seconds before each use.**
3. Hold the bottle firmly, as shown in Figure A, with your index and middle finger on either side of the spray tip and your thumb underneath the bottle.
4. Actuate the pump by QUICKLY and FIRMLY pressing down on the white collar while supporting the base of the bottle with your thumb.
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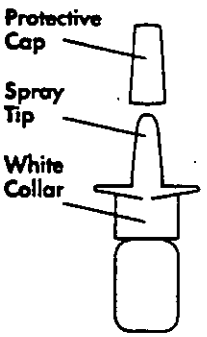
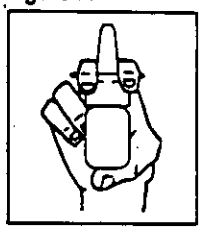


Figure A



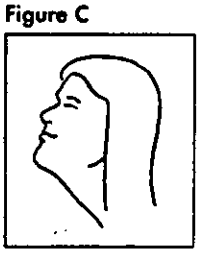
Instructions For Daily Use:

Follow these instructions for daily use of Rhinocort Aqua Nasal Spray:

1. Gently blow your nose to clear your nostrils, if necessary.
2. **Shake the bottle gently for a few seconds and remove the green protective cap.**
3. Hold the bottle firmly with your index and middle finger on either side of the spray tip and your thumb underneath the bottle (Figure A).
4. Insert the spray tip into your nostril (the tip should not reach far into your nose). Close the other nostril with a finger and lean your head slightly forward so the spray will aim toward the back of your nose (Figure B).
5. For each spray, actuate the pump by QUICKLY and FIRMLY pressing down on the white collar while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril.
6. After spraying into your nostril, lean your head backward for a few seconds (Figure C).
7. If a second spray is required in the same nostril, repeat steps 3 through 6.
8. Repeat steps 3 through 7 for your other nostril.
9. Avoid blowing your nose for 15 minutes after using Rhinocort Aqua Nasal Spray.
10. Wipe the spray tip with a clean tissue (Figure D), and replace the green protective cap. Store the bottle in an upright position.

Figure B

Figure C

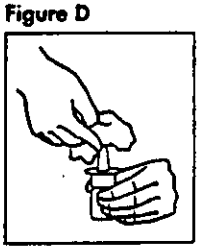


CLEANING

Rinse the upper plastic parts regularly. To do this:

1. Remove the green protective cap and lift off the spray tip.
2. Wash only these plastic parts in warm water and rinse them in cold tap water.
3. Allow the plastic parts to air-dry completely before reassembling the nasal spray.
4. If the spray tip becomes blocked, it can be cleared by performing the above steps. **DO NOT TRY TO UNBLOCK THE NASAL APPLICATOR BY USING A PIN OR OTHER SHARP OBJECT.**

Figure D



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Instructions for using your

Rhinocort® Aqua™ *(budesonide)* Nasal Spray 64 mcg

120 Metered Sprays

IMPORTANT: Please read this leaflet carefully before you start to use Rhinocort Aqua Nasal Spray. It provides a summary of information about your medicine. FOR FURTHER INFORMATION, ASK YOUR DOCTOR OR PHARMACIST.

WHAT YOU SHOULD KNOW ABOUT RHINOCORT AQUA NASAL SPRAY

Your doctor has prescribed Rhinocort Aqua Nasal Spray, a medicine that can help treat your nasal symptoms due to perennial or seasonal allergic rhinitis. Rhinocort Aqua Nasal Spray contains budesonide, a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. When you spray Rhinocort Aqua Nasal Spray into your nose, it helps to relieve or prevent your nasal stuffiness, itching, and sneezing that are caused by the inflammation.

BEFORE USING YOUR RHINOCORT AQUA NASAL SPRAY

BEFORE STARTING TO TAKE THIS MEDICINE, TELL YOUR DOCTOR:

- if you are pregnant (or intending to become pregnant),
- if you are breast-feeding a baby,
- if you are allergic to budesonide or any other nasal inhaled corticosteroid.

In some circumstances, this medicine may not be suitable, and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicine you are taking.

USING YOUR RHINOCORT AQUA NASAL SPRAY

- Follow the instructions on the reverse side of this page. If you have any problems, tell your doctor or pharmacist.
- It is important that you use Rhinocort Aqua Nasal Spray as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't or you are not sure how to use Rhinocort Aqua Nasal Spray, ask your doctor or pharmacist.

DOSAGE

- Use as directed by your doctor.
- It is VERY IMPORTANT that you follow your doctor's instructions as to how many sprays to take and how often to use your Rhinocort Aqua Nasal Spray.
- DO NOT take more doses or use Rhinocort Aqua Nasal Spray more often than your doctor tells you.
- IT IS VERY IMPORTANT THAT YOU USE RHINOCORT AQUA NASAL SPRAY REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE, EVEN IF YOU ARE FEELING BETTER, unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE the dose.
- If you also have itchy, watery eyes, you should tell your doctor. He or she can prescribe additional medication to treat these symptoms.

STORING YOUR RHINOCORT AQUA NASAL SPRAY

- Keep the green protective cap on Rhinocort Aqua Nasal Spray when not in use. (Please see Prior To Use on reverse side)
- Keep Rhinocort Aqua Nasal Spray and all medications **out of the reach of children.**
- Keep Rhinocort Aqua Nasal Spray in a dry place at controlled room temperature, 68 to 77°F (20 to 25°C). Do not freeze. Protect from light.
- Do not use Rhinocort Aqua Nasal Spray after 120 sprays (does not include priming) or after the expiration date shown on the carton.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medicine. If you have any questions, or are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

HOW TO USE YOUR RHINOCORT AQUA NASAL SPRAY

Read the complete instructions carefully and use only as directed.

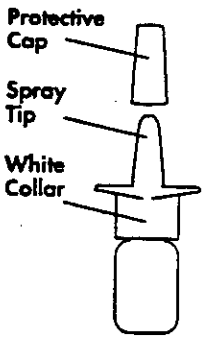
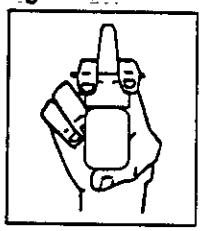


Figure A



Prior To Use:

Before using Rhinocort Aqua Nasal Spray for the first time, the bottle must be primed. To do this:

1. Pull to remove the green protective cap off the nasal spray unit.
2. **Shake the bottle gently for a few seconds before each use.**
3. Hold the bottle firmly, as shown in Figure A, with your index and middle finger on either side of the spray tip and your thumb underneath the bottle.
4. Actuate the pump by QUICKLY and FIRMLY pressing down on the white collar while supporting the base of the bottle with your thumb.
5. Prior to initial use, shake the bottle gently. The pump must be primed by actuating 8 times or until a fine spray appears. If used daily the pump does not need to be reprimed. If not used for 2 consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator using the cleaning steps listed below. Reprime with two sprays or until a fine spray appears.
6. Do not spray in eyes.

NOTE: Your Rhinocort Aqua Nasal Spray has been filled with an excess to accommodate the priming activity. The correct amount of medication in each spray cannot be assured after the labelled number of sprays even though the container is not completely empty. Keep track of the number of sprays released from the container.

Figure B

Instructions For Daily Use:

Follow these instructions for daily use of Rhinocort Aqua Nasal Spray:

1. Gently blow your nose to clear your nostrils, if necessary.
2. **Shake the bottle gently for a few seconds and remove the green protective cap.**
3. Hold the bottle firmly with your index and middle finger on either side of the spray tip and your thumb underneath the bottle (Figure A).
4. Insert the spray tip into your nostril (the tip should not reach far into your nose). Close the other nostril with a finger and lean your head slightly forward so the spray will aim toward the back of your nose (Figure B).
5. For each spray, actuate the pump by QUICKLY and FIRMLY pressing down on the white collar while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril.
6. After spraying into your nostril, lean your head backward for a few seconds (Figure C).
7. If a second spray is required in the same nostril, repeat steps 3 through 6.
8. Repeat steps 3 through 7 for your other nostril.
9. Avoid blowing your nose for 15 minutes after using Rhinocort Aqua Nasal Spray.
10. Wipe the spray tip with a clean tissue (Figure D), and replace the green protective cap. Store the bottle in an upright position.

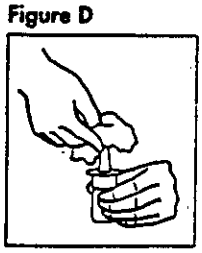
Figure C

CLEANING

Rinse the upper plastic parts regularly. To do this:

1. Remove the green protective cap and lift off the spray tip.
2. Wash only these plastic parts in warm water and rinse them in cold tap water.
3. Allow the plastic parts to air-dry completely before reassembling the nasal spray.
4. If the spray tip becomes blocked, it can be cleared by performing the above steps. **DO NOT TRY TO UNBLOCK THE NASAL APPLICATOR BY USING A PIN OR OTHER SHARP OBJECT.**

Figure D



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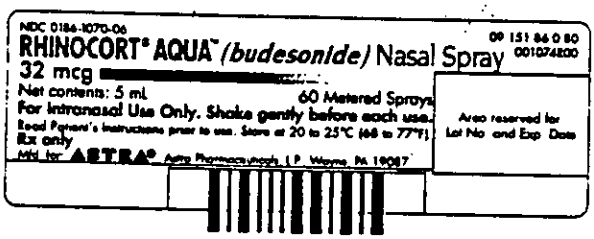

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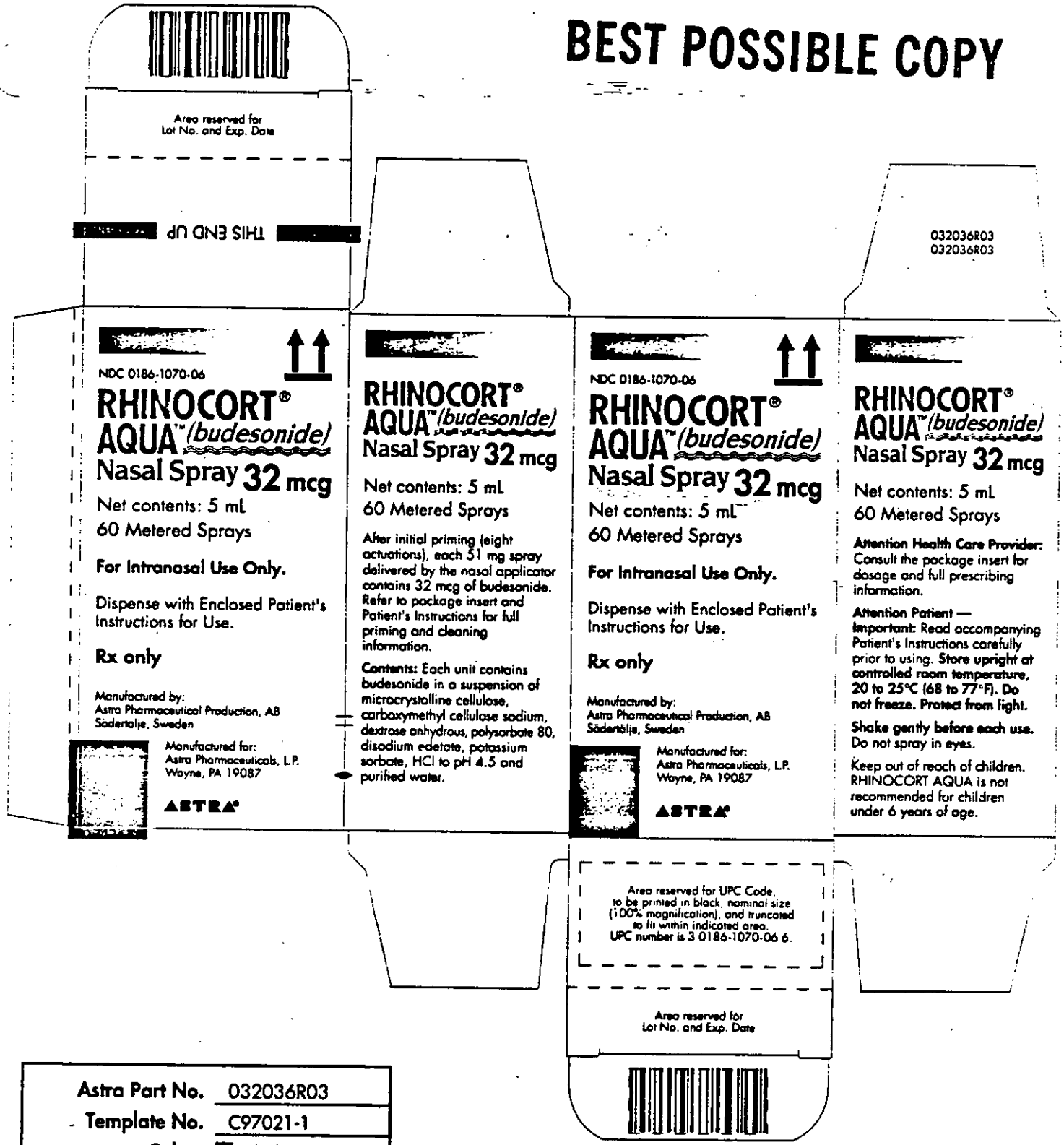

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NDC 0186-1070-06

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA®

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

After initial priming (eight actuations), each 51 mg spray delivered by the nasal applicator contains 32 mcg of budesonide. Refer to package insert and Patient's Instructions for full priming and cleaning information.

Contents: Each unit contains budesonide in a suspension of microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, HCl to pH 4.5 and purified water.

NDC 0186-1070-06

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA®

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 32 mcg

Net contents: 5 mL
60 Metered Sprays

Attention Health Care Provider: Consult the package insert for dosage and full prescribing information.

Attention Patient — Important: Read accompanying Patient's Instructions carefully prior to using. **Store upright at controlled room temperature, 20 to 25°C (68 to 77°F). Do not freeze. Protect from light.**

Shake gently before each use. Do not spray in eyes.

Keep out of reach of children. RHINOCORT AQUA is not recommended for children under 6 years of age.

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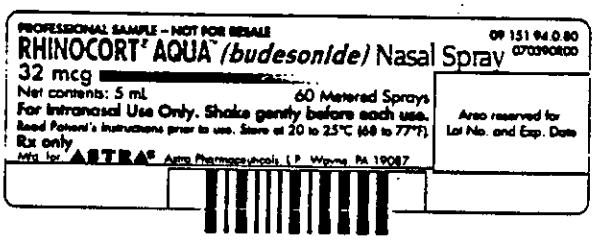

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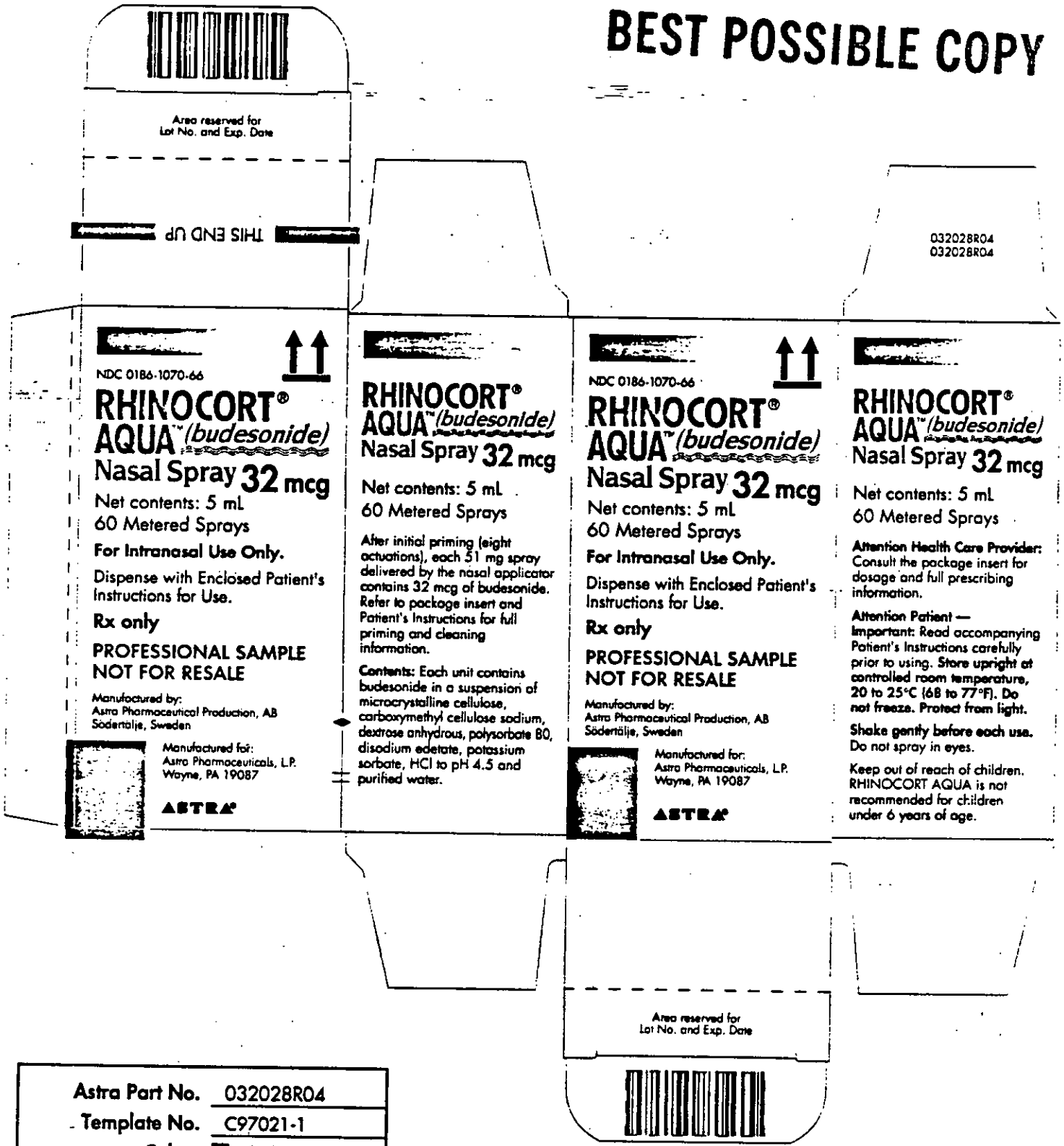

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Astra Pharmaceuticals

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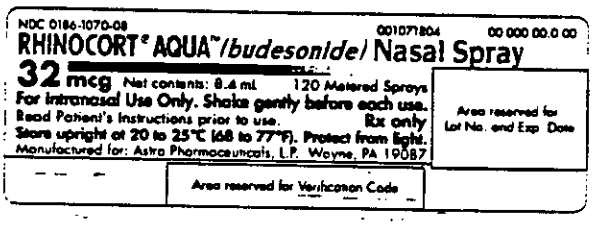

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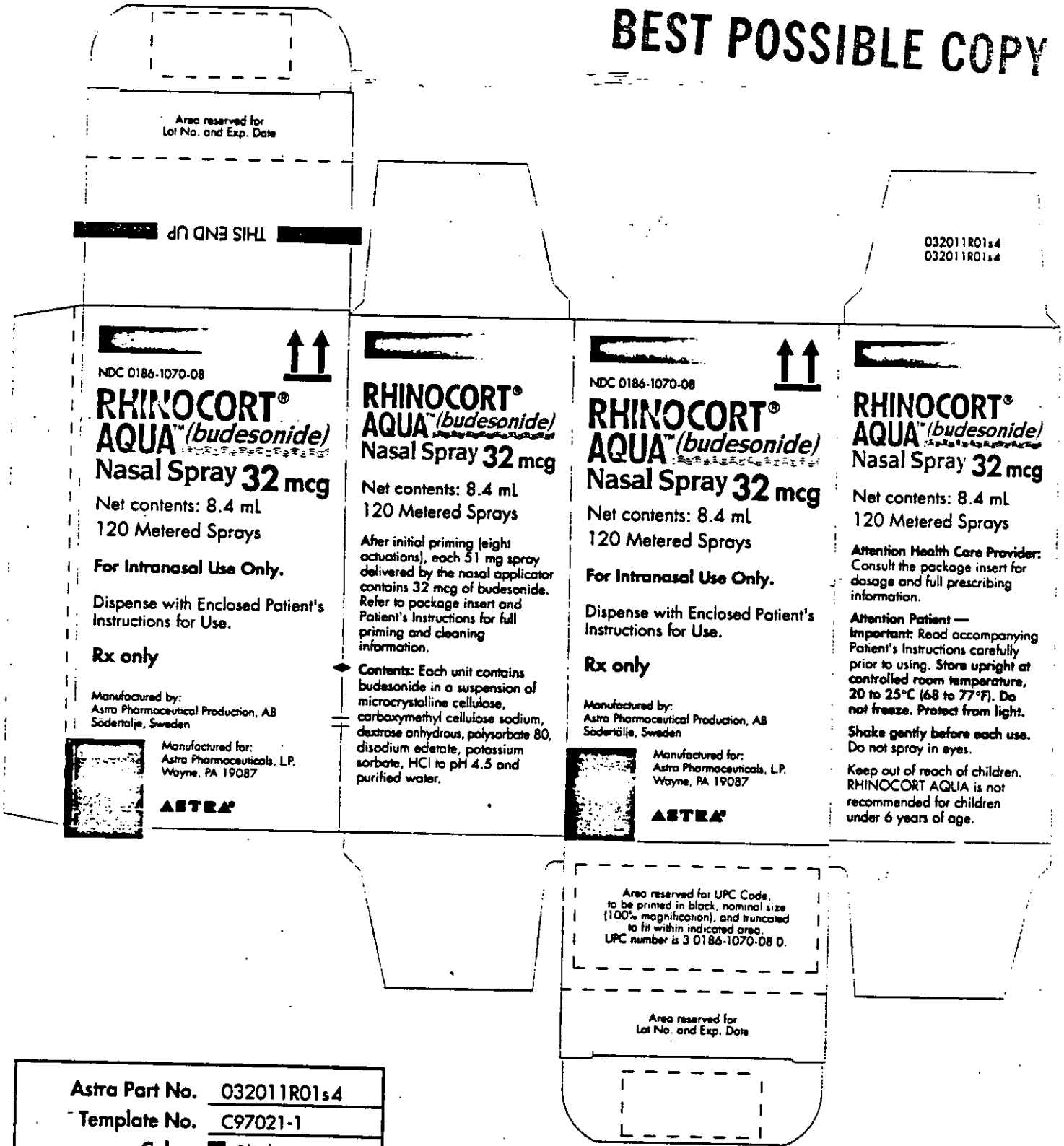

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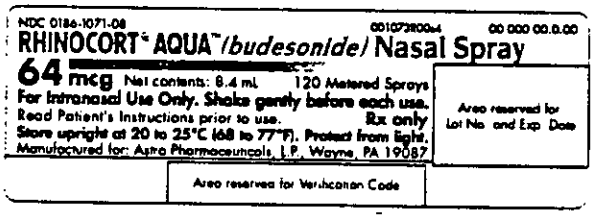

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NDC 0186-1071-08

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 64 mcg

Net contents: 8.4 mL
120 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA®

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 64 mcg

Net contents: 8.4 mL
120 Metered Sprays

After initial priming (eight actuations), each 51 mg spray delivered by the nasal applicator contains 64 mcg of budesonide. Refer to package insert and Patient's Instructions for full priming and cleaning information.

Contents: Each unit contains budesonide in a suspension of microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, HCl to pH 4.5 and purified water.

NDC 0186-1071-08

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 64 mcg

Net contents: 8.4 mL
120 Metered Sprays

For Intranasal Use Only.

Dispense with Enclosed Patient's Instructions for Use.

Rx only

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:
Astra Pharmaceuticals, L.P.
Wayne, PA 19087

ASTRA®

RHINOCORT® AQUA™ (budesonide)
Nasal Spray 64 mcg

Net contents: 8.4 mL
120 Metered Sprays

Attention Health Care Provider: Consult the package insert for dosage and full prescribing information.

Attention Patient — Important: Read accompanying Patient's Instructions carefully prior to using. **Store upright at controlled room temperature, 20 to 25°C (68 to 77°F). Do not freeze. Protect from light.**

Shake gently before each use. Do not spray in eyes.

Keep out of reach of children. RHINOCORT AQUA is not recommended for children under 6 years of age.

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