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C.1

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2000

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CONTENTS

RX GLAXO WELLCOME INC P. 1153

16.8-g canister
200 metered inhalations

Beclovent®
Inhalation Aerosol Refill
(beclomethasone dipropionate, USP)

RX GLAXO WELLCOME INC P. 1153

16.8-g canister
200 metered inhalations
Also available in a 6.7-g canister

Beconase®
Inhalation Aerosol
(beclomethasone dipropionate, USP)

RX GLAXO WELLCOME INC P. 1156

25 g

Beconase AQ®
Nasal Spray, 0.042%
(beclomethasone dipropionate, monohydrate)

RX GLAXO WELLCOME INC P. 1157

250 mg/5 mL
50 mL

250 mg/5 mL
100 mL

Also available in 50- and 100-mL bottles of 125 mg/5 mL.

Ceftin® for Oral Suspension
(cefuroxime axetil powder for oral suspension)

RX GLAXO WELLCOME INC P. 1157

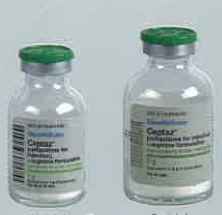
125 mg

250 mg

500 mg

Ceftin®
(cefuroxime axetil tablets)

RX GLAXO WELLCOME INC P. 1161



1-g vial 2-g vial

1-g IV infusion pack 2-g IV infusion pack

10-g
pharmacy bulk package

Ceptaz®
(ceftazidime for injection)
L-arginine formulation

RX GLAXO WELLCOME INC P. 1164

Combivir™
(lamivudine/zidovudine tablets)
150 mg/300 mg

RX GLAXO WELLCOME INC P. 1167

0.05% per 15 g

0.05% per 60 g
Also available in 30 g

Cutivate® Cream
(fluticasone propionate cream)

RX GLAXO WELLCOME INC P. 1168

0.005% per 15 g

0.005% per 60 g
Also available in 30 g

Cutivate® Ointment
(fluticasone propionate ointment)

RX GLAXO WELLCOME INC P. 1169

25 mg

Daraprim®
(pyrimethamine)

RX GLAXO WELLCOME INC P. 1170

38 mg

Digibind® Digoxin Immune Fab
(Ovine)

RX GLAXO WELLCOME INC P. 1171

2% per 27 g
Also available in 50 g

Emgel® 2% Topical Gel
(erythromycin)

RX GLAXO WELLCOME INC P. 1172

10 mg/1 mL
240 mL

Epivir® Oral Solution
(lamivudine oral solution)

RX GLAXO WELLCOME INC P. 1172

150 mg

Epivir®
(lamivudine tablets)

RX GLAXO WELLCOME INC P. 1175

100 mg

Epivir®-HBV™
(lamivudine)

RX GLAXO WELLCOME INC P. 1175

5 mg/1 mL
240 mL

Epivir®-HBV™ Oral Solution
(lamivudine)

RX GLAXO WELLCOME INC P. 1178

10 mL

Exosurf Neonatal® For Intratracheal Suspension
(colfosceril palmitate, cetyl alcohol, tyloxapol)

RX GLAXO WELLCOME INC P. 1181

0.5 mg/17 mL
Also available in 1.5 mg/17 mL

Flolan® for Injection
(epoprostenol sodium)

RX GLAXO WELLCOME INC P. 1158

16 g
120 metered sprays

Flonase® Nasal Spray, 50 mcg
(fluticasone propionate)

RX GLAXO WELLCOME INC P. 1186

13 g canister
120 metered inhalations
Also available in 7.9-g canister

Flovent® 44 mcg Inhalation Aerosol
(fluticasone propionate, 44 mcg)

RX GLAXO WELLCOME INC P. 1186

13-g canister
120 metered inhalations

Flovent® 110 mcg Inhalation Aerosol
(fluticasone propionate, 110 mcg)

While every effort has been made to reproduce products faithfully, this section is to be considered a quick reference identification aid. In cases of suspected overdosage, etc., chemical analysis of the product should be done.

RX GLAXO WELLCOME INC P. 1186

13-g canister
120 metered inhalations

Flovent® 220 mcg Inhalation Aerosol
(fluticasone propionate, 220 mcg)

RX GLAXO WELLCOME INC P. 1189

Flovent® Rotadisk® 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

RX GLAXO WELLCOME INC P. 1189

Flovent® Rotadisk® 100 mcg
(fluticasone propionate inhalation powder, 100 mcg)

RX GLAXO WELLCOME INC P. 1189

Flovent® Rotadisk® 250 mcg
(fluticasone propionate inhalation powder, 250 mcg)

RX GLAXO WELLCOME INC P. 1192

1 g/50 mL

2 g/50 mL

Fortaz®
(ceftazidime sodium injection)

OTC USANA P. 3142

90 tablets

Chelated Mineral
Dietary Supplement

OTC USANA P. 3142

30 soft-gel capsules

CoQuinone™
Dietary Supplement

OTC USANA P. 3142

90 tablets

Mega Antioxidant
Dietary Supplement

OTC USANA P. 3142

90 tablets

Proflavanol©
Dietary Supplement

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VIVUS, INC.

Ⓡ VIVUS, INC. P. 3143

ACTIS©
Venous Flow Controller

RX VIVUS, INC. P. 3143

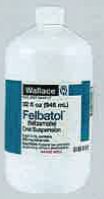
MUSE©
(alprostadil)

WALLACE LABORATORIES

RX WALLACE LABORATORIES P. 3147

137 mcg
Astelin©
Nasal Spray
(azelastine HCl)

RX WALLACE LABORATORIES P. 3151



600 mg/5 mL

600 mg
Felbatol©
(felbamate)

RX WALLACE LABORATORIES P. 3151

400 mg
Felbatol©
(felbamate)

RX WALLACE LABORATORIES P. 3157

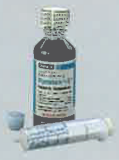
200 mg

100 mg/5 mL
Organidin© NR
(guaifenesin)

RX WALLACE LABORATORIES P. 3156

Rynatan©
(phenylephrine tannate, chlorpheniramine tannate, pyrilamine tannate)
25 mg / 8 mg / 25 mg

RX WALLACE LABORATORIES P. 3159



Rynatan©-S Pediatric Suspension
(phenylephrine tannate, chlorpheniramine tannate, pyrilamine tannate)
5 mg / 2 mg / 12.5 mg / 5 mL

RX WALLACE LABORATORIES P. 3160

Rynatuss©
(carbetapentane tannate, chlorpheniramine tannate, ephedrine tannate, phenylephrine tannate)

RX WALLACE LABORATORIES P. 3160

350 mg
Soma©
(carisoprodol)

RX WALLACE LABORATORIES P. 3161

Soma© Compound
(carisoprodol, aspirin)
200 mg / 325 mg

C-III WALLACE LABORATORIES P. 3161

Soma© Compound w/Codeine
(carisoprodol, aspirin, codeine phosphate)
200 mg / 325 mg / 16 mg

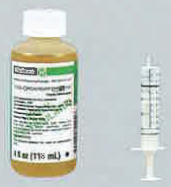
C-V WALLACE LABORATORIES P. 3163

Tussi-12™
(carbetapentane tannate, chlorpheniramine tannate, phenylephrine tannate)
30 mg / 4 mg / 5 mg per 5mL

C-V WALLACE LABORATORIES P. 3157

Tussi-Organidin©-S NR*
(guaifenesin, codeine phosphate)
100 mg / 10 mg / 5 mL
(* newly reformulated)

RX WALLACE LABORATORIES P. 3157

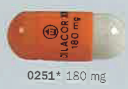


Tussi-Organidin© DM-S NR*
(guaifenesin, dextromethorphan HBr)
100 mg / 10 mg / 5 mL
(* newly reformulated)

WATSON

RX WATSON LABORATORIES INC. P. 3172

0252* 240 mg

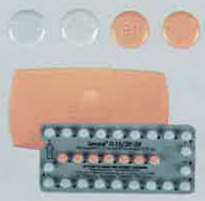


0251* 180 mg

0250* 120 mg

Dilacor XR©
(diltiazem HCl)
Extended-release Capsules

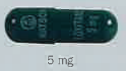
RX WATSON LABORATORIES INC. P. 3174



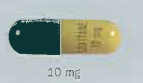
Also available in a 21 day unit without placebo tablets.

Levora©
(levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg)

RX WATSON LABORATORIES INC. P. 3177



5 mg



10 mg

25 mg

50 mg

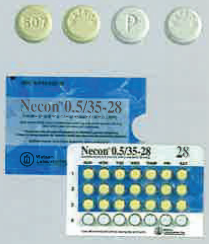
Loxitane©
(loxapine succinate)

RX WATSON LABORATORIES INC. P. 3179

12.5 mg

Microzide™
(hydrochlorothiazide)

RX WATSON LABORATORIES INC. P. 3180

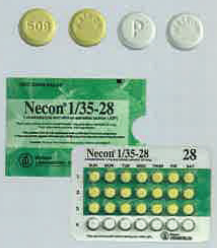


28-day

Also available in a 21 day unit without placebo tablets.

Necon© 0.5/35
(norethindrone and ethinyl estradiol tablets USP)
0.5 mg/35 mcg

RX WATSON LABORATORIES INC. P. 3180

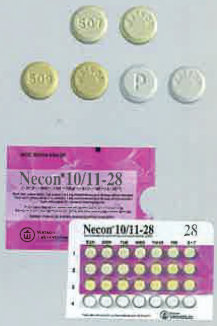


28-day

Also available in a 21 day unit without placebo tablets.

Necon© 1/35
(norethindrone and ethinyl estradiol tablets USP)
1 mg/35 mcg

RX WATSON LABORATORIES INC. P. 3180



28-day

Also available in a 21 day unit without placebo tablets.

Each light yellow tablet (10) contains 0.5 mg norethindrone and 35 mcg ethinyl estradiol. Each dark yellow tablet (11) contains 1 mg norethindrone and 35 mcg ethinyl estradiol. Each white tablet (7) contains inert ingredient.

Necon© 10/11
(norethindrone and ethinyl estradiol tablets USP)

Designed to help you identify drugs, this section contains actual size pills and full color reproduction of products selected for inclusion by participating manufacturers.

Flolan—Cont.

patible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. FLOLAN, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL. FLOLAN should be prepared using 2 vials of STERILE DILUENT for FLOLAN for use during a 24-hour period. Table 5 gives directions for preparing several different concentrations of FLOLAN:

[See table 5 below]

More than one solution strength may be required to accommodate the range of infusions anticipated during acute dose-ranging. Generally, 3000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg per minute in adults. Infusion rates may be calculated using the following formula:

$$\text{Infusion Rate (mL/hr)} = \frac{\text{[Dose (ng/kg/min)} \times \text{Weight (kg)} \times \text{60 min/hr]}}{\text{Final Concentration (ng/mL)}}$$

Tables 6 through 9 provide infusion delivery rates for doses up to 16 ng/kg per minute based upon patient weight, drug delivery rate, and concentration of the solution of FLOLAN to be used. These tables may be used to select the most appropriate concentration of FLOLAN that will result in an infusion rate between the minimum and maximum flow rates of the infusion pump and which will allow the desired duration of infusion from a given reservoir volume. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of FLOLAN.

Table 6: Infusion Rates for FLOLAN at a Concentration of 3000 ng/mL

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg per minute)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	1.2	1.6	2.0	2.4	2.8	3.2
20	—	1.6	2.4	3.2	4.0	4.8	5.6	6.4
30	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
40	1.6	3.2	4.8	6.4	8.0	9.6	11.2	12.8
50	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0
60	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
70	2.8	5.6	8.4	11.2	14.0	16.8	19.6	22.4
80	3.2	6.4	9.6	12.8	16.0	19.2	22.4	25.6
90	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
100	4.0	8.0	12.0	16.0	20.0	24.0	28.0	32.0

Table 7: Infusion Rates for FLOLAN at a Concentration of 5000 ng/mL

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg per minute)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	—	1.0	1.2	1.4	1.7	1.9
20	—	1.0	1.4	1.9	2.4	2.9	3.4	3.8
30	—	1.4	2.2	2.9	3.6	4.3	5.0	5.8
40	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
60	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4
80	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1	17.3
100	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2

Table 8: Infusion Rates for FLOLAN at a Concentration of 10,000 ng/mL

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg per minute)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	—	—	1.0	1.2	1.4	1.7	1.9
30	—	1.1	1.4	1.8	2.2	2.5	2.9
40	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	1.2	1.8	2.4	3.0	3.6	4.2	4.8
60	1.4	2.2	2.9	3.6	4.3	5.0	5.8
70	1.7	2.5	3.4	4.2	5.0	5.9	6.7
80	1.9	2.9	3.8	4.8	5.8	6.7	7.7
90	2.2	3.2	4.3	5.4	6.5	7.6	8.6
100	2.4	3.6	4.8	6.0	7.2	8.4	9.6

Table 9: Infusion Rates for FLOLAN at a Concentration of 15,000 ng/mL

Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg per minute)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
30	—	—	1.0	1.2	1.4	1.7	1.9
40	—	1.0	1.3	1.6	1.9	2.2	2.6
50	—	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.6	2.4	3.2	4.0	4.8	5.6	6.4

Storage and Stability: Unopened vials of FLOLAN are stable until the date indicated on the package when stored at 15° to 25°C (59° to 77°F) and protected from light in the carton. Unopened vials of STERILE DILUENT for FLOLAN are stable until the date indicated on the package when stored at 15° to 25°C (59° to 77°F).

Prior to use, reconstituted solutions of FLOLAN must be protected from light and must be refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. **Do not freeze reconstituted solutions of FLOLAN. Discard any reconstituted solution that has been frozen. Discard any reconstituted solution if it has been refrigerated for more than 48 hours.** During use, a single reservoir of reconstituted solution of FLOLAN can be administered at room temperature for a total duration of 8 hours, or it can be used with a cold pouch and administered up to 24 hours with the use of two frozen 6-oz gel packs in a cold pouch. When stored or in use, reconstituted FLOLAN must be insulated from temperatures greater than 25°C (77°F) and less than 0°C (32°F), and must not be exposed to direct sunlight.

Use at Room Temperature: Prior to use at room temperature, 15° to 25°C (59° to 77°F), reconstituted solutions of FLOLAN may be stored refrigerated at 2° to 8°C (36° to 46°F) for no longer than 40 hours. When administered at room temperature, reconstituted solutions may be used for no longer than 8 hours. This 48-hour period allows the patient to reconstitute a 2-day supply (200 mL) of FLOLAN. Each 100-mL daily supply may be divided into three equal portions. Two of the portions are stored refrigerated at 2° to 8°C (36° to 46°F) until they are used.

Use with a Cold Pouch: Prior to infusion with the use of a cold pouch, solutions may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. When a cold pouch is employed during the infusion, reconstituted solutions of FLOLAN may be used for no longer than 24 hours. The gel packs should be changed every 12 hours. Reconstituted solutions may be kept at 2° to 8°C (36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of the two, for no more than 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, FLOLAN should not be administered.

HOW SUPPLIED

FLOLAN for Injection is supplied as a sterile freeze-dried powder in 17-mL flint glass vials with gray butyl rubber closures, individually packaged in a carton.

17-mL vial containing epoprostenol sodium equivalent to 0.5 mg (500,000 ng), carton of 1 (NDC 0173-0517-00).

17-mL vial containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng), carton of 1 (NDC 0173-0519-00).

Store the vials of FLOLAN at 15° to 25°C (59° to 77°F). Protect from light.

The STERILE DILUENT for FLOLAN is supplied in 50-mL flint glass vials with fluororesin-faced butyl rubber closures.

50-mL vial of STERILE DILUENT for FLOLAN, tray of 4 (NDC 0173-0518-00).

Store the vials of STERILE DILUENT for FLOLAN at 15° to 25°C (59° to 77°F). DO NOT FREEZE.

US Patent Nos. 4,335,139; 4,539,333; and 4,883,812 (Use Patent)

Licensed Under US Patent No. 4,338,325

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

Sterile Diluent for FLOLAN manufactured by
Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

May 1998/RL-553

Shown in Product Identification Guide, page 313

Table 5

To make 100 mL of solution with final concentration (ng/mL) of:	Directions:
3000 ng/mL	Dissolve contents of one 0.5-mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw 3 mL and add to sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
5000 ng/mL	Dissolve contents of one 0.5-mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of two 0.5-mg vials each with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
*15,000 ng/mL**	Dissolve contents of one 1.5-mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.

* *Higher concentrations may be required for patients who receive FLOLAN long-term.*

FLONASE®

[flō'nāz]
(fluticasone propionate)
Nasal Spray, 50 mcg

For Intranasal Use Only.
SHAKE GENTLY BEFORE USE.

DESCRIPTION

Fluticasone propionate, the active ingredient of FLONASE Nasal Spray, is a synthetic corticosteroid with the chemical name of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLONASE Nasal Spray 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was threefold to fivefold more potent than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (see Pharmacokinetics) is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In seven trials in adults, FLONASE Nasal Spray has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct relationship of these findings to long-term symptom relief is not known.

FLONASE Nasal Spray, like other corticosteroids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not be reached for several days. Similarly, when corticosteroids are discontinued, symptoms may not return for several days.

Pharmacokinetics: ***Absorption:*** The activity of FLONASE Nasal Spray is due to the parent drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue

binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg three times daily) did not affect fluticasone propionate pharmacokinetics.

In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1000 mcg, 5 times the maximum daily intranasal dose) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Excretion: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Fluticasone propionate was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Pharmacodynamics: In a trial to evaluate the potential systemic and topical effects of FLONASE Nasal Spray on allergic rhinitis symptoms, the benefits of comparable drug blood levels produced by FLONASE Nasal Spray and oral fluticasone propionate were compared. The doses used were 200 mcg of FLONASE Nasal Spray, the nasal spray vehicle (plus oral placebo), and 5 and 10 mg of oral fluticasone propionate (plus nasal spray vehicle) per day for 14 days. Plasma levels were undetectable in the majority of patients after intranasal dosing, but present at low levels in the majority after oral dosing. FLONASE Nasal Spray was significantly more effective in reducing symptoms of allergic rhinitis than either the oral fluticasone propionate or the nasal vehicle. This trial demonstrated that the therapeutic effect of FLONASE Nasal Spray can be attributed to the topical effects of fluticasone propionate.

In another trial, the potential systemic effects of FLONASE Nasal Spray on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. FLONASE Nasal Spray given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. FLONASE Nasal Spray at either dose for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both doses of oral prednisone significantly reduced the response to cosyntropin.

Clinical Trials: A total of 13 randomized, double-blind, parallel, multicenter, vehicle-controlled clinical trials were conducted in the United States in adults and pediatric patients (4 years of age and older) with seasonal or perennial allergic rhinitis. The trials included 2633 adults (1439 men and 1194 women) with a mean age of 37 years (range, 18 to 79). A total of 440 adolescents (405 boys and 35 girls), mean age of 14 (range, 12 to 17), and 500 children (325 boys and 175 girls), mean age of 9 (range, 4 to 11) were also studied. The overall racial distribution was 89% white, 4% black, and 7% other. These trials evaluated the total nasal symptom scores (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for 2 to 24 weeks. Subjects treated with FLONASE Nasal Spray exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients. Nasal mucosal basophils and eosinophils were also reduced at the end of treatment in adult studies; however, the clinical significance of this decrease is not known.

There were no significant differences between fluticasone propionate regimens whether administered as a single daily dose of 200 mcg (two 50-mcg sprays in each nostril) or as 100 mcg (one 50-mcg spray in each nostril) twice daily in six clinical trials. A clear dose response could not be identified in clinical trials. In one trial, 200 mcg/day was slightly more effective than 50 mcg/day during the first few days of treatment; thereafter, no difference was seen.

Three randomized, double-blind, parallel, vehicle-controlled trials were conducted in 1191 patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated total nasal symptom scores (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and in one of the 3 trials for 6 months of open-label treatment. Two of these trials demonstrated that patients treated with FLONASE Nasal Spray at a dose of 100 mcg twice daily exhibited statistically significant decreases in total nasal symptom scores compared with patients treated with vehicle.

Individualization of Dosage: Adult patients may be started on a 200-mcg once-a-day regimen (two 50-mcg sprays in each nostril once-a-day). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice-a-day).

Individual patients will experience a variable time to onset and different degree of symptom relief. In 4 randomized, double-blind, placebo-controlled, parallel group allergic rhinitis studies and 2 studies of patients in an outdoor "park" setting (park studies), a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment with a 200-mcg dose of FLONASE Nasal Spray. Maximum effect may take several days. Patients who have responded may be able to be maintained (after 4 to 7 days) on 100 mcg/day (one spray in each nostril once daily).

Pediatric patients (4 years of age and older) should be started with 100 mcg (one spray in each nostril once-a-day). Treatment with 200 mcg (two sprays in each nostril once daily or one spray in each nostril twice daily) should be reserved for pediatric patients not adequately responding to 100 mcg daily. Once adequate control is achieved, the dosage should be decreased to 100 mcg (one spray in each nostril) daily.

Maximum total daily doses should not exceed two sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

INDICATIONS AND USAGE

FLONASE Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been adequately established.

CONTRAINDICATIONS

FLONASE Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

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 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.

The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

Patients who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in patients on immunosuppressant doses of corticosteroids. In such patients 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 chickenpox, 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 chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General: Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of FLONASE Nasal Spray. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including fluticasone propionate.

Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism, suppression of HPA function, and/or reduction of growth velocity in children or teenagers. Physicians should closely follow the growth of children and adolescents taking corticosteroids, by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed.

Although systemic effects have been minimal with recommended doses of FLONASE Nasal Spray, potential risk increases with larger doses. Therefore, larger than recommended doses of FLONASE Nasal Spray should be avoided. When used at higher than recommended doses, or in rare individuals at recommended doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of FLONASE Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with fluticasone propionate 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 therapy and discontinuation of treatment with FLONASE Nasal Spray. Patients using FLONASE 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. FLONASE Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection; untreated local or systemic fungal or bacterial, or systemic viral infections or parasitic infection; 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.

Information for Patients: Patients being treated with FLONASE Nasal Spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should use FLONASE Nasal Spray at regular intervals as directed since its effectiveness depends on its regular use. A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with FLONASE Nasal Spray. Results in several clinical trials indicate statistically significant improvement within the first day or two of treatment; however, the full benefit of FLONASE Nasal Spray may not be achieved until treatment has been administered for several days. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens. For the proper use of the nasal spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions accompanying the product.

Drug Interactions: In a placebo-controlled, crossover study in eight healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1000 mcg, 5 times the maximum daily intranasal dose) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased mean fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. This interaction may be due to an inhibition of the cytochrome P450 3A4 isoenzyme system by ketoconazole, which is also the route of metabolism of fluticasone propionate. No drug interaction studies have been conducted with FLONASE Nasal Spray; however, care should be exercised when fluticasone propionate is coadministered with long-term ketoconazole and other known cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults and approximately equivalent to the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Pregnancy: *Teratogenic Effects*: Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to and 4 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis, respectively) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rab-

Continued on next page

This product information is based on labeling in effect on June 10, 1999. For further information, contact via direct mail, phone, or web site Medical Information: Glaxo Wellcome Inc., PO Box 13398, Research Triangle Park, NC 27709. Healthcare Professionals (Medical Information): 800-334-0089 Patients (Customer Response Center): 888-TALK2GW (1-888-825-5249) Glaxo Wellcome Corporate Web Site: www.glaxowellcome.com

Flonase—Cont.

bits (approximately 4 and 25 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m² basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate 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.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. When tritiated fluticasone propionate was administered to rats at a subcutaneous dose of 10 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m² basis), radioactivity was excreted in the milk. Because other corticosteroids are excreted in human milk, caution should be exercised when FLONASE Nasal Spray is administered to a nursing woman.

Pediatric Use: Five hundred (500) patients aged 4 to 11 years of age and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established.

Oral and, to a less clear extent, inhaled and intranasal corticosteroids have been shown to have the potential to cause a reduction in growth velocity in children and adolescents with extended use. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: A limited number of patients above 60 years of age (n = 275) have been treated with FLONASE Nasal Spray in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients.

ADVERSE REACTIONS

In controlled US studies, more than 3300 patients with seasonal allergic, perennial allergic, or perennial nonallergic rhinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with approximately the same frequency by patients treated with the vehicle itself. The complaints did not usually interfere with treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle placebo and active comparators. Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6 months' duration with FLONASE Nasal Spray. If recommended doses are exceeded, however, or if individuals are particularly sensitive, or taking FLONASE Nasal Spray in conjunction with administration of other corticosteroids, symptoms of hypercorticism, e.g., Cushing's syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon seven controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 2 to 4 weeks and two controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated with FLONASE Nasal Spray 200 mcg once daily over 6 months. Also included in the table are adverse events from two studies in which 167 children (45 girls and 122 boys aged 4 to 11 years) were treated with FLONASE Nasal Spray 100 mcg once daily for 2 to 4 weeks. [See table below]

Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common with fluticasone propionate (with uncertain relationship to treatment) included: blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to fluticasone propionate, occurrence during clinical trials, or a combination of these factors.

General: Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear, Nose, and Throat: Alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and voice changes.

Eye: Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

OVERDOSAGE

Chronic overdosage with FLONASE Nasal Spray may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since one bottle of FLONASE Nasal Spray contains approximately 8 mg of fluticasone propionate.

The oral and subcutaneous median lethal doses in mice and rats were >1000 mg/kg (>20000 and >41000 times, respectively, the maximum recommended daily intranasal dose in adults and >10000 and >20000 times, respectively, the maximum recommended daily intranasal dose in children on a mg/m² basis).

DOSAGE AND ADMINISTRATION

Patients should use FLONASE Nasal Spray at regular intervals as directed since its effectiveness depends on its regular use.

Adults: The recommended starting dosage in **adults** is two sprays (50 mcg of fluticasone propionate each) in each nostril once-a-day (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice-a-day (e.g., 8 a.m. and 8 p.m.) is also effective. After the first few days, patients may be able to reduce their dosage to 100 mcg (one spray in each nostril) once daily for maintenance therapy.

Adolescents and Children (4 Years of Age and Older): Patients should be started with 100 mcg (one spray in each nostril once-a-day). Patients not adequately responding to 100 mcg may use 200 mcg (two sprays in each nostril). Once adequate control is achieved, the dosage should be decreased to 100 mcg (one spray in each nostril) daily.

The maximum total daily dosage should not exceed two sprays in each nostril (200 mcg/day). (See Individualization of Dosage and Clinical Trials sections.)

FLONASE Nasal Spray is not recommended for children under 4 years of age.

Directions for Use: Illustrated patient's instructions for proper use accompany each package of FLONASE Nasal Spray.

HOW SUPPLIED

FLONASE Nasal Spray 50 mcg is supplied in an amber glass bottle providing 120 actuations, net fill weight 16 g (NDC 0173-0453-01). Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The bottle should be discarded when the labeled number of actuations has been reached even though the bottle is not completely empty. Each bottle is fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of one with patient's instructions for use.

Store between 4° and 30°C (39° and 86°F).

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

U.S. Patent 4,335,121

INSEAL™ is covered by the following Inprint Systems patent applications:

European 94916311.7, Canada 2140025, USA 08/373,213.

December 1998/RL-645

Shown in Product Identification Guide, page 313

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With FLONASE Nasal Spray in Patients ≥4 Years With Seasonal or Perennial Allergic Rhinitis

	Vehicle Placebo (n = 758) %	FLONASE 100 mcg Once Daily (n = 167) %	FLONASE 200 mcg Once Daily (n = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Nasal burning/irritation	2.6	2.4	3.2
Nausea/vomiting	2.0	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

FLOVENT® 44 mcg
(fluticasone propionate, 44 mcg)
Inhalation Aerosol

FLOVENT® 110 mcg
(fluticasone propionate, 110 mcg)
Inhalation Aerosol

FLOVENT® 220 mcg
(fluticasone propionate, 220 mcg)
Inhalation Aerosol

For Oral Inhalation Only

DESCRIPTION

The active component of FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, and FLOVENT 220 mcg Inhalation Aerosol is fluticasone propionate, a glucocorticoid having the chemical name S-(fluoromethyl)-6,9-difluoro-11β, 17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate.

Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, and FLOVENT 220 mcg Inhalation Aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in a mixture of two chlorofluorocarbon propellants (trichloromonofluoromethane and dichlorodifluoromethane) with lecithin. Each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate from the valve, and 44, 110, or 220 mcg, respectively, of fluticasone propionate from the actuator.

CLINICAL PHARMACOLOGY

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of glucocorticoid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Glucocorticoids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of glucocorticoids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, glucocorticoids do not affect asthma symptoms immediately. However, improvement following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When glucocorticoids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics: ***Absorption:*** The activity of FLOVENT Inhalation Aerosol is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and pre-systemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation aerosol in healthy volunteers averaged about 30% of the dose delivered from the actuator. Peak plasma concentrations after an 800-mcg inhaled dose ranged from 0.1 to 1.0 ng/mL.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had approximately 2,000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special populations. In a clinical study using fluticasone propi-

MUCO-FEN® 800 DM TABLETS ℞

[mū-co-fin]
Guaifenesin/Dextromehorphan HBr

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Guaifenesin ..... 800 mg
Dextromethorphan Hydrobromide ..... 60 mg

DOSAGE
Adults and children over 12 years of age: 1 tablet every 12 hours not to exceed 2 tablets in 24 hours
Children 6–12 years of age: ½ tablet every 12 hours not to exceed 1 tablet in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-114-10)

MUCO-FEN® 800 Tablets ℞

[mū-co-fin]
Guaifenesin

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Guaifenesin ..... 800 mg

DOSAGE
Adults and children over 12 years of age: 1–1½ tablets every 12 hours not to exceed 3 tablets (2400 mg) in 24 hours
Children 6–12 years of age: ½ tablet every 12 hours not to exceed 1200 mg in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-109-10)

MUCO-FEN® 1200 TABLETS ℞

[mū-co-fin]
Guaifenesin

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Guaifenesin ..... 1200 mg

DOSAGE
Adults and children over 12 years of age: 1 tablet every 12 hours not to exceed 2 tablets (2400 mg) in 24 hours
Children 6–12 years of age: ½ tablet every 12 hours not to exceed 1 tablet (1200 mg) in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-120-10)

MUCO-FEN® DM TABLETS ℞

[mū-co-fin]
Guaifenesin/Dextromethorphan HBr

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Guaifenesin ..... 600 mg
Dextromethorphan Hydrobromide ..... 30 mg

DOSAGE
Adults and children over 12 years of age: 1–2 tablets every 12 hours not to exceed 4 tablets in 24 hours
Children 6–12 years of age: 1 tablet every 12 hours not to exceed 2 tablets in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-108-10)

MUCO-FEN® LA Tablets ℞

[mū-co-fin]
Guaifenesin

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Guaifenesin ..... 600 mg

DOSAGE
Adults and children over 12 years of age: 1–2 tablets every 12 hours not to exceed 4 tablets (2400 mg) in 24 hours
Children 6–12 years of age: 1 tablet every 12 hours not to exceed 2 tablets (1200 mg) in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-102-10)

PROFEN LA® TABLETS ℞

[prō'-fin]
Phenylpropanolamine HCl/Guaifenesin

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Phenylpropanolamine Hydrochloride ..... 75 mg
Guaifenesin ..... 600 mg

DOSAGE
Adults and children over 12 years of age: 1 tablet every 12 hours
Children 6–12 years of age: ½ tablet every 12 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-104-10)

PROFEN II® TABLETS ℞

[prō'-fin]
Phenylpropanolamine HCl/Guaifenesin

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Phenylpropanolamine Hydrochloride ..... 37.5 mg
Guaifenesin ..... 600 mg

DOSAGE
Adults and children over 12 years of age: 1–2 tablets every 12 hours not to exceed 4 tablets in 24 hours
Children 6–12 years of age: 1 tablet every 12 hours not to exceed 2 tablets in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-107-10)

PROFEN II DM® Liquid ℞

[prō'-fin]
Dextromethorphan HBr/Phenylpropanolamine HCl/Guaifenesin

DESCRIPTION
Each 5 mL (one teaspoonful) of PROFEN II DM® LIQUID contains:
Dextromethorphan HBr ..... 10 mg
Phenylpropanolamine HCl ..... 12.5 mg
Guaifenesin ..... 200 mg
In a sugar free, dye free and alcohol free base.

DOSAGE
Adults and children 12 years or older: 1–2 teaspoonfuls every 4 hours not to exceed 12 teaspoonfuls in 24 hours. Children 6–12 years of age: ½–1 teaspoonful every 4 hours not to exceed 6 teaspoonfuls in 24 hours. Children 2–6 years of age: ⅓–½ teaspoonful not to exceed 3 teaspoonfuls in 24 hours. Children under 2 years: As directed by physician.

HOW SUPPLIED
PROFEN II DM® LIQUID is available as a sugar, alcohol and dye-free clear liquid having a cherry odor and flavor.
Pint Bottles: NDC 59310-201-16.

PROFEN II DM® TABLETS ℞

[prō'-fin]
Dextromethorphan HBr/Phenylpropanolamine HCl/Guaifenesin

DESCRIPTION
Each time-released, dye free, scored tablet contains:
Dextromethorphan Hydrobromide ..... 30 mg
Phenylpropanolamine Hydrochloride ..... 37.5 mg
Guaifenesin ..... 600 mg

DOSAGE
Adults and children over 12 years of age: 1–2 tablets every 12 hours not to exceed 4 tablets in 24 hours
Children 6–12 years of age: 1 tablet every 12 hours not to exceed 2 tablets in 24 hours

HOW SUPPLIED
Bottles of 100 tablets (NDC 59310-110-10)

Wallace Laboratories
P.O. BOX 1001
CRANBURY, NJ 08512

For Medical Information, Contact:
Generally:
Professional Services
800-526-3840
After Hours and Weekend Emergencies:
(609) 655-6474

Wallace Laboratories
Sales and Ordering:
Div. of Carter-Wallace, Inc
P.O. Box 1001
Cranbury, NJ 08512

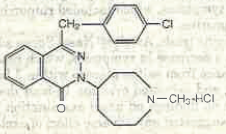
AQUATENSEN® ℞

(methyclothiazide tablets, USP, 5 mg)
Tablets

ASTELIN® ℞

(azelastine hydrochloride)
Nasal Spray, 137 mcg
For Intranasal Use Only

DESCRIPTION
Astelin® (azelastine hydrochloride) Nasal Spray, 137 micrograms (mcg), is an antihistamine formulated as a metered-spray solution for intranasal administration. Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is $C_{22}H_{24}ClN_3O{\cdot}HCl$ with the following chemical structure:



Astelin® Nasal Spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 ± 0.3. It also contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.
After priming, each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base). Each bottle can deliver 100 metered sprays.

CLINICAL PHARMACOLOGY
Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1-receptor antagonist activity in isolated tissues, animal models, and humans. Astelin® Nasal Spray is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in *in vitro* studies. The major metabolite, desmethylazelastine, also possesses H_1-receptor antagonist activity.

Pharmacokinetics and Metabolism
After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (Cmax) are achieved in 2–3 hours. Based on intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized to the principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythromycin failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimetidine (400 mg twice daily), a nosnpecific P450 inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.
The major active metabolite, desmethylazelastine, was not measurable (below assay limits) after single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing of azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine range from 20–50% of azelastine concentrations. When azelastine hydrochloride is administered orally, desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranasal or oral route.
In vitro studies with human plasma indicate that the plasma protein binding of azelastine and desmethylazelastine are approximately 88% and 97%, respectively.
Azelastine hydrochloride administered intranasally at doses above two sprays per nostril twice daily for 29 days resulted in greater than proportional increases in Cmax and area under the curve (AUC) for azelastine.
Studies in healthy subjects administered oral doses of azelastine hydrochloride demonstrated linear responses in Cmax and AUC.

Special Populations
Following oral administration, pharmacokinetic parameters were not influenced by age, gender, or hepatic impairment. Based on oral, single-dose studies, renal insufficiency (creatine clearance <50 mL/min) resulted in a 70–75% higher Cmax and AUC compared to normal subjects. Time to maximum concentration was unchanged.
Oral azelastine has been safely administered to over 1400 asthmatic subjects, supporting the safety of administering Astelin® Nasal Spray to allergic rhinitis patients with asthma.

Pharmacodynamics
In a placebo-controlled study (95 subjects with allergic rhinitis), there was no evidence of an effect of Astelin® Nasal Spray (2 sprays per nostril twice daily for 56 days) on car-

Continued on next page

Astelin—Cont.

diac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram. At higher oral exposures (≥4 mg twice daily), a nonclinically significant mean change in the QTc (3–7 millisecond increase) was observed. Interaction studies investigating the cardiac repolarization effects of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or QTc based on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement of azelastine plasma levels; however, no effects on QTc were observed (see PRECAUTIONS, Drug Interactions).

Clinical Trials

U.S. placebo-controlled clinical trials of Astelin® Nasal Spray included 322 patients with seasonal allergic rhinitis who received two sprays per nostril twice a day for up to 4 weeks. These trials included 55 pediatric patients ages 12 to 16 years. Astelin® Nasal Spray significantly improved a complex of symptoms, which included rhinorrhea, sneezing, and nasal pruritis.

In dose-ranging trials, Astelin® Nasal Spray administration resulted in a decrease in symptoms, which reached statistical significance from saline placebo within 3 hours after initial dosing and persisted over the 12-hour dosing interval. There were no findings on nasal examination in an 8-week study that suggested any adverse effect of azelastine on the nasal mucosa.

INDICATIONS AND USAGE

Astelin® Nasal Spray is indicated for the treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults and children 12 years and older.

CONTRAINDICATIONS

Astelin® Nasal Spray is contraindicated in patients with a known hypersensitivity to azelastine hydrochloride or any of its components.

PRECAUTIONS

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking Astelin® Nasal Spray; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of Astelin® Nasal Spray with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Information for Patients: Patients should be instructed to use Astelin® Nasal Spray only as prescribed. For the proper use of the nasal spray and to attain maximum improvement, the patient should read and follow carefully the accompanying patient instructions. Patients should be instructed to prime the delivery system before initial use and after storage for 3 or more days (see PATIENT INSTRUCTIONS FOR USE). Patients should also be instructed to store the bottle upright at room temperature with the pump tightly closed and out of the reach of children. In case of accidental ingestion by a young child, seek professional assistance or contact a poison control center immediately.

Patients should be advised against the concurrent use of Astelin® Nasal Spray with other antihistamines without consulting a physician. Patients who are, or may become, pregnant should be told that this product should be used in pregnancy or during lactation only if the potential benefit justifies the potential risks to the fetus or nursing infant. Patients should be advised to assess their individual responses to Astelin® Nasal Spray before engaging in any activity requiring mental alertness, such as driving a car or operating machinery. Patients should be advised that the concurrent use of Astelin® Nasal Spray with alcohol or other CNS depressants may lead to additional reductions in alertness and impairment of CNS performance and should be avoided (see Drug Interactions).

Drug Interactions: Concurrent use of Astelin® Nasal Spray with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Cimetidine (400 mg twice daily) increased the mean Cmax and AUC of orally administered azelastine hydrochloride (4 mg twice daily) by approximately 65%. Ranitidine hydrochloride (150 mg twice daily) had no effect on azelastine pharmacokinetics.

Interaction studies investigating the cardiac effects, as measured by the corrected QT interval (QTc), of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. Oral erythromycin (500 mg three times daily for seven days) had no effect on azelastine pharmacokinetics or QTc based on analyses of serial electrocardiograms. Ketoconazole (200 mg twice daily for seven days) interfered with the measurement of azelastine plasma concentrations; however, no effects on QTc were observed.

No significant pharmacokinetic interaction was observed with the coadministration of an oral 4 mg dose of azelastine hydrochloride twice daily and theophylline 300 mg or 400 mg twice daily.

Geriatric Use: U.S. placebo-controlled clinical trials included 11 patients above the age of 60 years who were treated with Astelin® Nasal Spray. While this number is very small and no substantial conclusions can be drawn, the adverse events in this group were similar to patients under age 60 years.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies in rats and mice with oral azelastine hydrochloride for 24 months at doses up to 30 mg/kg/day and 25 mg/kg/day, respectively (240 and 100 times the maximum recommended human daily intranasal dose on a mg/m^2 basis), revealed no evidence of carcinogenicity.

Azelastine hydrochloride showed no genotoxic effects in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in rat bone marrow.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 30 mg/kg/day (240 times the maximum recommended human daily intranasal dose on a mg/m^2 basis). At 68.6 mg/kg/day (550 times the maximum recommended human daily intranasal dose on a mg/m^2 basis), the duration of estrous cycles was prolonged and copulatory activity and the number of pregnancies were decreased. The numbers of corpora lutea and implantations were decreased; however, the implantation ratio was not affected.

Pregnancy Category C: Azelastine hydrochloride has been shown to be embryotoxic, fetotoxic, and teratogenic (external and skeletal abnormalities) in mice at an oral dose of 68.6 mg/kg/day (280 times the maximum recommended human daily intranasal dose on a mg/m^2 basis).

At an oral dose of 30 mg/kg/day (240 times the maximum recommended human daily intranasal dose on a mg/m^2 basis), delayed ossification (undeveloped metacarpus), and the incidence of 14th rib were increased in rats. At 68.6 mg/kg/day (550 times the maximum recommended human daily intranasal dose on a mg/m^2 basis) azelastine hydrochloride caused abortion and fetotoxic effects in rats.

The relevance to humans of these skeletal findings noted at only high drug exposure levels is unknown.

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

Nursing Mothers: It is not known whether azelastine hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Astelin® Nasal Spray is administered to a nursing woman.

Pediatric Use: Safety and efficacy of Astelin® Nasal Spray in pediatric patients below the age of 12 years have not been established.

ADVERSE REACTIONS

Adverse experience information for Astelin® Nasal Spray is derived from six well-controlled, 2-day to 8-week clinical studies which included 391 patients who received Astelin® Nasal Spray at a dose of 2 sprays per nostril twice daily. In placebo-controlled efficacy trials, the incidence of discontinuation due to adverse reactions in patients receiving Astelin® Nasal Spray was not significantly different from vehicle placebo (2.2% vs 2.8%, respectively).

In these clinical studies, adverse events that occurred statistically significantly more often in patients treated with Astelin® Nasal Spray versus vehicle placebo included bitter taste (19.7% vs 0.6%), somnolence (11.5% vs 5.4%), weight increase (2.0% vs 0%), and myalgia (1.5% vs 0%).

The following adverse events were reported with frequencies ≥2% in the Astelin® Nasal Spray treatment group and more frequently than placebo in short-term (≤2 days) and long-term (2–8 weeks) clinical trials.

ADVERSE EVENT	Astelin® Nasal Spray n=391	Vehicle Placebo n=353
Bitter Taste*	19.7	0.6
Headache	14.8	12.7
Somnolence*	11.5	5.4
Nasal Burning	4.1	1.7
Pharyngitis	3.8	2.8
Dry Mouth	2.8	1.7
Paroxysmal Sneezing	3.1	1.1
Nausea	2.8	1.1
Rhinitis	2.3	1.4
Fatigue	2.3	1.4
Dizziness	2.0	1.4
Epistaxis	2.0	1.4
Weight Increase*	2.0	0.0

*$P<0.05$, Fisher's Exact Test (two-tailed)

The following events were observed infrequently (<2% and exceeding placebo incidence) in patients who received Astelin® Nasal Spray (2 sprays/nostril twice daily) in U.S. clinical trials.

Cardiovascular: flushing, hypertension, tachycardia.

Dermatological: contact dermatitis, eczema, hair and follicle infection, furunculosis.

Digestive: constipation, gastroenteritis, glossitis, ulcerative stomatitis, vomiting, increased SGPT, aphthous stomatitis.

Metabolic and Nutritional: increased appetite.

Musculoskeletal: myalgia, temporomandibular dislocation.

Neurological: hyperkinesia, hypoesthesia, vertigo.

Psychological: anxiety, depersonalization, depression, nervousness, sleep disorder, thinking abnormal.

Respiratory: bronchospasm, coughing, throat burning, laryngitis.

Special Senses: conjunctivitis, eye abnormality, eye pain, watery eyes, taste loss.

Urogenital: albuminuria, amenorrhea, breast pain, hematuria, increased urinary frequency.

Whole Body: allergic reaction, back pain, herpes simplex, viral infection, malaise, pain in extremities, abdominal pain.

In controlled trials involving nasal and oral azelastine hydrochloride formulations, there were infrequent occurrences of hepatic transaminase elevations. The clinical relevance of these reports has not been established.

In addition, the following spontaneous adverse events have been reported during the marketing of Astelin® Nasal Spray and causal relationship with the drug is unknown: anaphylactoid reaction, application site irritation, chest pain, nasal congestion, confusion, diarrhea, dyspnea, facial edema, involuntary muscle contractions, paresthesia, parosmia, pruritus, rash, tolerance, urinary retention, vision abnormal, and xerophthalmia.

OVERDOSAGE

There have been no reported overdosages with Astelin® Nasal Spray. Acute overdosage by adults with this dosage form is unlikely to result in clinically significant adverse events, other than increased somnolence, since one bottle of Astelin® Nasal Spray contains 17 mg of azelastine hydrochloride. Clinical studies in adults with single doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events. General supportive measures should be employed if overdosage occurs. There is no known antidote to Astelin® Nasal Spray. Oral ingestion of antihistamines has the potential to cause serious adverse effects in young children. Accordingly, Astelin® Nasal Spray should be kept out of the reach of children. Oral doses greater than 120 mg/kg (480 times the maximum recommended human daily intranasal dose on a mg/m^2 basis) produced significant mortality in mice. Responses seen prior to mortality were tremor, convulsions, decreased muscle tone, and salivation. Single doses as high as 10 mg/kg (270 times the maximum recommended human daily intranasal dose on a mg/m^2 basis) were well tolerated in dogs, but single doses of 20 mg/kg were lethal.

DOSAGE AND ADMINISTRATION

The recommended dose of Astelin® Nasal Spray in adults and children 12 years and older is two sprays per nostril twice daily. Before initial use, the screw cap on the bottle should be replaced with the pump unit and the delivery system should be primed with 4 sprays or until a fine mist appears. When 3 or more days have elapsed since the last use, the pump should be reprimed with 2 sprays or until a fine mist appears.

CAUTION: Avoid spraying in the eyes.

Directions for Use: Illustrated patient instructions for proper use accompany each package of Astelin® Nasal Spray.

HOW SUPPLIED

Astelin® (azelastine hydrochloride) Nasal Spray, 137 mcg (NDC 0037-0241-10) is supplied as a package containing a total of 200 metered sprays in two high-density polyethylene (HDPE) bottles fitted with screw caps. A separate metered-dose spray pump unit and a leaflet of patient instructions are also provided. The spray pump unit is packaged in a polyethylene wrapper and consists of a nasal spray pump fitted with a blue safety clip and a blue plastic dust cover. Each Astelin® (azelastine hydrochloride) Nasal Spray, 137 mcg, bottle contains 17 mg (1 mg/mL) of azelastine hydrochloride to be used with the supplied metered-dose spray pump unit. Each bottle can deliver 100 metered sprays. Each spray delivers a mean of 0.137 mL solution containing 137 mcg of azelastine hydrochloride.

ATTENTION: The imprinted expiration date applies to the product in the bottles with screw caps. After the spray pump is inserted into the first bottle of the dispensing package, both bottles of product should be discarded after 3 months, not to exceed the expiration date imprinted on the label.

Storage: Store at controlled room temperature 20°–25°C (68°–77°F). Protect from freezing.

Manufactured by
Wallace Laboratories
Division of Carter-Wallace, Inc.
Cranbury, NJ 08512-0181 for
Wallace Laboratories/ASTA Medica LLC

IN-023S3-08A Rev. 1/99

Shown in Product Identification Guide, page 341

DEPEN® Ⓡ
(penicillamine tablets, USP)
Titratable Tablets

Physicians planning to use penicillamine should thoroughly familiarize themselves with its toxicity, special