

PATANASE Nasal Spray (S-002) Alcon Proposed Labeling Text

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PATANASE[®] Nasal Spray safely and effectively. See full prescribing information for PATANASE Nasal Spray.

PATANASE (olopatadine hydrochloride) Nasal Spray

Initial U.S. Approval: 1996

-----INDICATIONS AND USAGE-----

PATANASE Nasal Spray is an H₁ receptor antagonist indicated for the relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older. (1)

-----DOSAGE AND ADMINISTRATION-----

For intranasal use only.

Recommended dosages:

- Adults and adolescents ≥ 12 years: Two sprays per nostril twice daily. (2.1)
- Children 6 to 11 years: One spray per nostril twice daily. (2.2)

Priming Information: Prime PATANASE Nasal Spray before initial use and when PATANASE Nasal Spray has not been used for more than 7 days. (2.3)

-----DOSAGE FORMS AND STRENGTHS-----

Nasal spray 0.6%: 665 mcg of olopatadine hydrochloride in each 100- microliter spray. (3) Supplied as a 30.5 g bottle containing 240 sprays.

-----CONTRAINDICATIONS-----

None.

-----WARNINGS AND PRECAUTIONS-----

- Epistaxis, nasal ulceration, and nasal septal perforation. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Discontinue if ulcerations or perforations occur. Avoid use in patients with nasal disease other than allergic rhinitis (5.1).
- Avoid engaging in hazardous occupations requiring complete mental alertness and coordination such as driving or operating machinery when taking PATANASE Nasal Spray (5.2).
- Avoid concurrent use of alcohol or other central nervous system depressants with PATANASE Nasal Spray (5.2).

-----ADVERSE REACTIONS-----

The most common (>1%) adverse reactions included bitter taste, headache, epistaxis, pharyngolaryngeal pain, post-nasal drip, cough, and urinary tract infection in patients 12 years of age and older and epistaxis, headache, upper respiratory tract infection, bitter taste, pyrexia, and rash in patients 6 to 11 years of age (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: xxxx

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Seasonal Allergic Rhinitis: PATANASE Nasal Spray is an H₁ receptor antagonist indicated for the relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

Administer PATANASE Nasal Spray by the intranasal route only.

2.1 Adults and Adolescents 12 years of age and older: The recommended dosage is two sprays per nostril twice daily.

2.2 Children 6 to 11 years of age: The recommended dosage is one spray per nostril twice daily.

2.3 Administration Information

Priming: Before initial use, prime PATANASE Nasal Spray by releasing 5 sprays or until a fine mist appears. When PATANASE Nasal Spray has not been used for more than 7 days, re-prime by releasing 2 sprays. Avoid spraying PATANASE Nasal Spray into the eyes.

3 DOSAGE FORMS AND STRENGTHS

PATANASE Nasal Spray is a nasal spray solution supplied in a white plastic bottle with a metered-dose manual spray pump, a white nasal applicator, and a blue overcap. Each spray (100 microliters) delivers 665 mcg of olopatadine hydrochloride.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

Epistaxis and Nasal Ulceration: In placebo (vehicle nasal spray)-controlled clinical trials of 2 weeks to 12 months duration, epistaxis and nasal ulcerations were reported [*see Adverse Reactions (6)*].

Nasal Septal Perforation:

Two placebo (vehicle nasal spray)-controlled long term (12 months) safety trials were conducted. In the first safety trial, patients were treated with an investigational formulation of PATANASE Nasal Spray containing povidone (not the commercially marketed formulation) or a vehicle nasal spray containing povidone. Nasal septal perforations were reported in one patient treated with the investigational formulation of PATANASE Nasal Spray and 2 patients treated with the vehicle nasal spray. In the second safety trial with PATANASE Nasal Spray, which does not contain povidone, there were no reports of nasal septal perforation [*see Adverse Reactions (6)*].

Before starting PATANASE Nasal Spray, conduct a nasal examination to ensure that patients are free of nasal disease other than allergic rhinitis. Perform nasal examinations periodically for signs of adverse effects on the nasal mucosa and consider stopping PATANASE Nasal Spray if patients develop nasal ulcerations.

5.2 Activities Requiring Mental Alertness

In clinical trials, the occurrence of somnolence has been reported in some patients taking PATANASE Nasal Spray [*see Adverse Reactions (6)*]. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as driving or operating machinery after administration of PATANASE Nasal Spray. Concurrent use of PATANASE Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.

6 ADVERSE REACTIONS

Use of PATANASE Nasal Spray has been associated with epistaxis, nasal ulcerations, and somnolence [*see Warnings and Precautions (5.1 and 5.2)*].

6.1 Clinical Trials Experience

The safety data described below reflect exposure to PATANASE Nasal Spray in 2,427 patients with seasonal or perennial allergic rhinitis in 9 controlled clinical trials of 2 weeks to 12 months duration.

The safety data from adults and adolescents are based upon 5 placebo (vehicle nasal spray)-controlled clinical trials in which 1,491 patients with seasonal or perennial allergic rhinitis (513 males and 978 females) 12 years of age and older were treated with PATANASE Nasal Spray two sprays per nostril twice daily. There were 1,180 patients (PATANASE Nasal Spray, 587; vehicle nasal spray, 593) that participated in 3 efficacy and safety trials of 2 weeks duration. There were 1,814 patients (PATANASE Nasal Spray, 904; vehicle nasal spray, 910) that participated in 2 long-term clinical trials of 1 year duration. The racial distribution of adult and adolescent patients receiving PATANASE Nasal Spray was 76% white, 8% black, 12% Hispanic and 3% other. The incidence of discontinuation due to adverse reactions in these controlled clinical trials was comparable for PATANASE Nasal Spray and vehicle nasal spray. Overall, 3.9% of the 1,491 adult and adolescent patients across all 5 studies treated with PATANASE Nasal Spray and 3.2% of the 1,503 patients treated with vehicle nasal spray discontinued due to adverse reactions.

The safety data from pediatric patients 6-11 years of age are based upon 3 clinical trials in which 870 children with seasonal allergic rhinitis (376 females and 494 males) were treated with PATANASE Nasal

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Spray 1 or 2 sprays per nostril twice daily for 2 weeks. The racial distribution of pediatric patients receiving PATANASE Nasal Spray was 68.6% white, 16.6% black, and 14.8% other. The incidence of discontinuation due to adverse reactions in these controlled clinical trials was comparable for PATANASE Nasal Spray and vehicle nasal spray. Overall, 1.4% of the 870 pediatric patients across all 3 studies treated with PATANASE Nasal Spray and 1.3% of the 872 pediatric patients treated with vehicle nasal spray discontinued due to adverse reactions. Safety information for pediatric patients 2 to 5 years of age is obtained from one vehicle-controlled study of 2 weeks duration [*See Pediatric Use (8.4)*].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults and Adolescents 12 Years of Age and Older in Short-Term (2-week) Trials:

There were 1,180 patients 12 years of age and older (PATANASE Nasal Spray, 587; vehicle nasal spray, 593) that participated in 3 efficacy and safety trials of 2 weeks duration. Table 1 presents the most common adverse reactions (0.9% or greater in patients treated with PATANASE Nasal Spray) that occurred more frequently in patients treated with PATANASE Nasal Spray compared with vehicle nasal spray in the 3 clinical trials of 2 weeks duration.

Table 1: Adverse Reactions Occurring at an Incidence of 0.9% or Greater in Controlled Clinical Trials of 2 Weeks Duration with PATANASE Nasal Spray in Adolescent and Adult Patients 12 Years of Age and Older with Seasonal Allergic Rhinitis

Adverse Reaction	Adult and Adolescent Patients 12 Years and Older	
	PATANASE Nasal Spray N = 587	Vehicle Nasal Spray N = 593
Bitter taste	75 (12.8%)	5 (0.8%)
Headache	26 (4.4%)	24 (4.0%)
Epistaxis	19 (3.2%)	10 (1.7%)
Pharyngolaryngeal Pain	13 (2.2%)	8 (1.3%)
Post-nasal drip	9 (1.5%)	5 (0.8%)
Cough	8 (1.4%)	3 (0.5%)
Urinary tract infection	7 (1.2%)	3 (0.5%)
CPK elevation	5 (0.9%)	2 (0.3%)
Dry mouth	5 (0.9%)	1 (0.2%)
Fatigue	5 (0.9%)	4 (0.7%)
Influenza	5 (0.9%)	1 (0.2%)
Nasopharyngitis	5 (0.9%)	4 (0.7%)
Somnolence	5 (0.9%)	2 (0.3%)
Throat irritation	5 (0.9%)	0 (0.0%)

There were no differences in the incidence of adverse reactions based on gender or race. Clinical trials did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger subjects.

Pediatric Patients 6 to 11 Years of Age: There were 1,742 pediatric patients 6 to 11 years of age (Olopatadine nasal spray, 870; vehicle nasal spray, 872) with seasonal allergic rhinitis that participated in 3 clinical trials of 2 weeks duration. Two of the studies used the investigational formulation of olopatadine nasal spray, and one of the studies used PATANASE Nasal Spray. One study evaluated the safety of PATANASE Nasal Spray at doses of 1 and 2 sprays per nostril twice daily in 1188 patients, in which 298 were exposed to PATANASE 1 spray, 296 were exposed to PATANASE 2 sprays, 297 were exposed to vehicle 1 spray, and 297 were exposed to vehicle 2 sprays twice daily for 2 weeks. Table 2 presents the most common adverse reactions (greater than 1.0% in pediatric patients 6-11 years of age treated with PATANASE Nasal Spray 1 spray/nostril) that occurred more frequently with PATANASE Nasal Spray compared with vehicle nasal spray.

Table 2. Adverse Reactions Occurring at an Incidence of Greater than 1.0% in a Controlled Clinical Trial of 2 Weeks Duration with PATANASE Nasal Spray in Pediatric Patients 6-11 Years of Age With Seasonal Allergic Rhinitis

Adverse Reaction	Pediatric Patients 6 to 11 Years of Age	
	PATANASE Nasal Spray 1 spray per nostril N = 298	Vehicle Nasal Spray 1 spray per nostril N = 297
Epistaxis	17 (5.7%)	11 (3.7%)
Headache	13 (4.4%)	11 (3.7%)
Upper respiratory tract infection	8 (2.6%)	0
Bitter taste	3 (1.0%)	0
Pyrexia	4 (1.3%)	3 (1.0%)
Rash	4 (1.3%)	0

There were no differences in the incidence of adverse reactions based on gender, race, or ethnicity.

The safety of PATANASE Nasal Spray at a dose of 1 spray per nostril twice daily was evaluated in one 2-week vehicle-controlled study in 132 patients (PATANASE Nasal Spray, 66; vehicle nasal spray, 66) 2 to 5 years of age with allergic rhinitis [*see Pediatric Use (8.4)*].

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Long-Term (12-month) Safety Trials:

In a 12-month, placebo (vehicle nasal spray)-controlled, safety trial, 890 patients 12 years of age and older with perennial allergic rhinitis were randomized to treatment with PATANASE Nasal Spray 2 sprays per nostril twice daily (445 patients) or vehicle nasal spray (445 patients). In the PATANASE and vehicle nasal spray groups, 72% and 74% of patients, respectively, completed the trial. Overall, 7% and 5%, respectively, discontinued study participation due to an adverse event. The most frequently reported adverse reaction was epistaxis, which occurred in 25% of patients treated with PATANASE Nasal Spray and 28% in patients treated with vehicle nasal spray. Epistaxis resulted in discontinuation of 0.9% of patients treated with PATANASE Nasal Spray and 0.2% of patients treated with vehicle nasal spray. Nasal ulcerations occurred in 10% of patients treated with PATANASE Nasal Spray and 9% of patients treated with vehicle nasal spray. Nasal ulcerations resulted in discontinuation of 0.4% of patients treated with PATANASE Nasal Spray and 0.2% patients treated with vehicle nasal spray. There were no patients with nasal septal perforation in either treatment group. Somnolence was reported in 1 patient treated with PATANASE Nasal Spray and 1 patient treated with vehicle nasal spray. Weight increase was reported in 6 patients treated with PATANASE Nasal Spray and 1 patient treated with vehicle nasal spray. Depression or worsening of depression occurred in 9 patients treated with PATANASE Nasal Spray and in 5 patients treated with vehicle nasal spray. Three patients, two of whom had pre-existing histories of depression, who received PATANASE NASAL SPRAY were hospitalized for depression compared to none who received vehicle nasal spray.

In a second 12-month, placebo (vehicle nasal spray)-controlled, safety trial, 459 patients 12 years of age and older with perennial allergic rhinitis were treated with 2 sprays per nostril of an investigational formulation of PATANASE Nasal Spray containing povidone (not the commercially marketed formulation) and 465 patients were treated with 2 sprays of a vehicle nasal spray containing povidone. Nasal septal perforations were reported in one patient treated with the investigational formulation of PATANASE Nasal Spray and 2 patients treated with the vehicle nasal spray. Epistaxis was reported in 19% of patients treated with the investigational formulation of PATANASE Nasal Spray and 12% of patients treated with vehicle nasal spray. Somnolence was reported in 3 patients treated with the investigational formulation of PATANASE Nasal Spray compared to 1 patient treated with vehicle nasal spray. Fatigue was reported in 5 patients treated with the investigational formulation of PATANASE Nasal Spray compared to 1 patient treated with vehicle nasal spray.

There were no long-term clinical trials in children below 12 years of age.

6.2 Post-Marketing Experience

The post-marketing adverse events reported post-approval are consistent with the adverse events reported during clinical trials. Because post-marketing adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Formal drug-drug interaction studies were not conducted for PATANASE Nasal Spray. Drug interactions with inhibitors of liver enzymes are not anticipated because olopatadine is eliminated predominantly by renal excretion. Drug interactions involving P450 inhibition and plasma protein binding are also not expected. [See *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

No adequate and well-controlled studies in pregnant women have been conducted. Animal reproductive studies in rats and rabbits revealed treatment-related effects on fetuses or pups. Because animal studies are not always predictive of human responses, PATANASE Nasal Spray should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

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A decrease in the number of live fetuses was observed in rabbits and rats at the oral olopatadine doses approximately 88 times and 100 times the maximum recommended human dose (MRHD) and above, respectively, for adults on a mg/m² basis. In rats, viability and body weights of pups were reduced on day 4 post partum at the oral dose approximately 100 times the MRHD for adults on a mg/m² basis, but no effect on viability was observed at the dose approximately 35 times the MRHD for adults on a mg/m² basis.

8.3 Nursing Mothers

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical nasal administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk. PATANASE Nasal Spray should be used by nursing mothers only if the potential benefit to the patient outweighs the potential risks to the infant.

8.4 Pediatric Use

The safety and effectiveness of PATANASE Nasal Spray has not been established for patients under 6 years of age. The safety of olopatadine nasal spray was evaluated in 3 vehicle-controlled 2-week studies in 870 patients 6 to 11 years of age [see *Adverse Reactions* (6.1)]. Doses studied included 1 and 2 sprays per nostril twice daily. One of these studies evaluated the safety of PATANASE Nasal Spray at doses of 1 and 2 sprays per nostril twice daily in 1188 patients, of which, 298 patients were exposed to PATANASE 1 spray and 297 patients were exposed to vehicle 1 spray. In this study, the incidence of epistaxis with PATANASE treatment was 5.7%, compared to 3.2% seen in adult and adolescent studies. This study also evaluated the effectiveness of PATANASE Nasal Spray in patients 6 through 11 years of age with seasonal allergic rhinitis [see *Clinical Studies* (14.1)].

The safety of PATANASE Nasal Spray at a dose of 1 spray per nostril twice daily was evaluated in one 2-week vehicle-controlled study in 132 children ages 2 to 5 years of age with allergic rhinitis. In this trial, 66 patients (28 females and 38 males) were exposed to PATANASE Nasal Spray. The racial distribution of patients receiving PATANASE Nasal Spray was 66.7% white, 27.3% black, and 6.4% other. Two patients exposed to vehicle nasal spray discontinued due to an adverse reaction (1 patient with pneumonia and 1 patient with rhinitis) compared to no patients exposed to PATANASE Nasal Spray. The most common (greater than 1.0%) adverse events reported were diarrhea (9.1%), epistaxis (6.1%), rhinorrhea (4.5%), bitter taste (3.0%) and wheezing (3.0%). Diarrhea was reported less frequently (< 1%) in the 6 to 11 year old age group.

The incidence of epistaxis was higher in the pediatric population (5.7% in 6 -11 year old patients and 6.1% in 2-5 year old patients) compared to the adult and adolescent population (3.2%).

8.5 Geriatric Use

Clinical studies of PATANASE Nasal Spray did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There have been no reported overdosages with PATANASE Nasal Spray.

Acute overdose with this dosage form is unlikely due to the configuration of the primary container closure system. However, symptoms of antihistamine overdose may include drowsiness in adults and, initially, agitation and restlessness, followed by drowsiness in children. There is no known specific antidote to PATANASE Nasal Spray. Should overdose occur, symptomatic or supportive treatment is recommended, taking into account any concomitantly ingested medications.

No mortality was observed in rats at an intranasal dose of 3.6 mg/kg (approximately 6 times the MRHD for adults and adolescents \geq 12 years of age and 7 times the MRHD for children 6-11 years of age on a mg/m² basis), or in dogs at an oral dose of 5 g/kg (approximately 28,000 times the MRHD for adults and

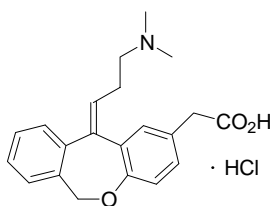
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adolescents ≥ 12 years of age and 33,000 the MRHD for children 6-11 years of age on a mg/m^2 basis). The oral median lethal dose (MLD) in mice and rats were 1,490 mg/kg and 3,870 mg/kg respectively (approximately 1,200 times and 6,500 times the MRHD for adults and adolescents ≥ 12 years of age and 1,500 times and 7,700 times the MRHD for children 6-11 years of age, on a mg/m^2 basis, respectively).

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION

PATANASE (olopatadine hydrochloride) Nasal Spray, 665 micrograms (mcg) is a metered-spray solution for intranasal administration. Olopatadine hydrochloride, the active component of PATANASE Nasal Spray, is a white, water-soluble crystalline powder. The chemical name for olopatadine hydrochloride is (Z)-11-[3-(dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride. It has a molecular weight of 373.88, and its molecular formula is $\text{C}_{21}\text{H}_{23}\text{NO}_3 \cdot \text{HCl}$ with the following chemical structure:



PATANASE Nasal Spray contains 0.6% w/v olopatadine (base) in a nonsterile aqueous solution with pH of approximately 3.7. After initial priming (5 sprays), each metered spray from the nasal applicator delivers 100 microliters of the aqueous solution containing 665 mcg of olopatadine hydrochloride, which is equivalent to 600 mcg of olopatadine (base) [see *Dosage and Administration*]. PATANASE Nasal Spray also contains benzalkonium chloride (0.01%), dibasic sodium phosphate, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olopatadine is a histamine H_1 -receptor antagonist. The antihistaminic activity of olopatadine has been documented in isolated tissues, animal models, and humans.

12.2 Pharmacodynamics

Cardiac effects: In a placebo-controlled cardiovascular safety study, 32 healthy volunteers received 20 mg oral solution of olopatadine twice daily for 14 days (8-fold greater daily dose than the recommended daily nasal dose). The mean QTcF (QT corrected by Fridericia's correction method for heart rate) change from baseline was -2.7 msec and -3.8 msec for olopatadine, and placebo, respectively. In this study, 8 subjects treated with olopatadine had a QTcF change from baseline of 30 – 60 msec, 1 subject had a QTcF change from baseline greater than 60 msec, and no subjects had QTcF values greater than 500 msec. Eight subjects treated with placebo had a QTcF change from baseline of 30 – 60 msec, no subjects had a QTcF change from baseline greater than 60 msec, and no subjects had QTcF values greater than 500 msec. In a 12-month study in 429 perennial allergic rhinitis patients treated with PATANASE Nasal Spray 2 sprays per nostril twice daily, no evidence of any effect of olopatadine hydrochloride on QT prolongation was observed.

12.3 Pharmacokinetics

The pharmacokinetic properties of olopatadine were studied after administration by the nasal, oral, intravenous, and topical ocular routes. Olopatadine exhibited linear pharmacokinetics across the routes studied over a large dose range.

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Absorption:

Healthy Subjects: Olopatadine was absorbed with individual peak plasma concentrations observed between 30 minutes and 1 hour after twice daily intranasal administration of PATANASE Nasal Spray. The mean (\pm SD) steady-state peak plasma concentration (C_{\max}) of olopatadine was 16.0 ± 8.99 ng/mL. Systemic exposure as indexed by area under the curve (AUC_{0-12}) averaged 66.0 ± 26.8 ng·h/mL. The average absolute bioavailability of intranasal olopatadine is 57%. The mean accumulation ratio following multiple intranasal administration of PATANASE Nasal Spray was about 1.3.

Seasonal Allergic Rhinitis (SAR) Patients: Systemic exposure of olopatadine in SAR patients after twice daily intranasal administration of PATANASE Nasal Spray was comparable to that observed in healthy subjects. Olopatadine was absorbed with peak plasma concentrations observed between 15 minutes and 2 hours. The mean steady-state C_{\max} was 23.3 ± 6.2 ng/mL and AUC_{0-12} averaged 78.0 ± 13.9 ng·h/mL.

Distribution: The protein binding of olopatadine was moderate at approximately 55% in human serum, and independent of drug concentration over the range of 0.1 to 1000 ng/mL. Olopatadine was bound predominately to human serum albumin.

Metabolism: Olopatadine is not extensively metabolized. Based on plasma metabolite profiles following oral administration of [14 C] olopatadine, at least six minor metabolites circulate in human plasma. Olopatadine accounts for 77% of peak plasma total radioactivity and all metabolites amounted to <6% combined. Two of these have been identified as the olopatadine N-oxide and N-desmethyl olopatadine. In *in vitro* studies with cDNA-expressed human cytochrome P450 isoenzymes (CYP) and flavin-containing monooxygenases (FMO), N-desmethyl olopatadine (M1) formation was catalyzed mainly by CYP3A4, while olopatadine N-oxide (M3) was primarily catalyzed by FMO1 and FMO3. Olopatadine at concentrations up to 33,900 ng/mL did not inhibit the *in vitro* metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The potential for olopatadine and its metabolites to act as inducers of CYP enzymes has not been evaluated.

Elimination: The plasma elimination half-life of olopatadine is 8 to 12 hours. Olopatadine is mainly eliminated through urinary excretion. Approximately 70% of a [14 C] olopatadine hydrochloride oral dose was recovered in urine with 17% in the feces. Of the drug-related material recovered within the first 24 hours in the urine, 86% was unchanged olopatadine with the balance comprised of olopatadine N-oxide and N-desmethyl olopatadine.

Special Population:

Hepatic Impairment: No specific pharmacokinetic study examining the effect of hepatic impairment was conducted. Since metabolism of olopatadine is a minor route of elimination, no adjustment of the dosing regimen of PATANASE Nasal Spray is warranted in patients with hepatic impairment.

Renal Impairment: The mean C_{\max} values for olopatadine following single intranasal doses were not markedly different between healthy subjects (18.1 ng/mL) and patients with mild, moderate and severe renal impairment (range 15.5 to 21.6 ng/mL). Mean plasma AUC_{0-12} was two-fold higher in patients with severe impairment (creatinine clearance <30 mL/min/1.73 m²). In these patients, peak steady-state plasma concentrations of olopatadine are approximately 10-fold lower than those observed after higher 20 mg oral doses, twice daily, which were well-tolerated. These findings indicate that no adjustment of the dosing regimen of PATANASE Nasal Spray is warranted in patients with renal impairment.

Gender: The mean systemic exposure (C_{\max} and AUC_{0-12}) in female SAR patients following multiple administration of olopatadine was 40% and 27% higher, respectively than those values observed in male SAR patients.

Race: The effects of race on olopatadine pharmacokinetics have not been adequately investigated.

Age: Pediatric Patients 6 to 11 Years of Age: The systemic pharmacokinetics of olopatadine, olopatadine N-oxide and N-desmethyl olopatadine in patients 6 through 11 years of age were characterized using data

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from 42 pediatric patients administered PATANASE Nasal Spray, one spray per nostril twice daily for a minimum of 14 days. The mean C_{max} (15.4 ± 7.3 ng/mL) of olopatadine was approximately 2-fold less than was comparable to that observed in adults (78.0 ± 13.9 ng·h/mL). The C_{max} and AUC_{0-12} of olopatadine N-oxide were comparable to that observed in adults. The C_{max} and AUC_{0-12} of N-desmethyl olopatadine are approximately 18% and 37% higher than that observed in adults, respectively.

Pediatric Patients 2 to 5 Years of Age: The systemic pharmacokinetics of olopatadine, olopatadine N-oxide, and N-desmethyl olopatadine were characterized using population pharmacokinetic methods applied to sparse data (approximately 5 samples per patient) obtained from 66 pediatric patients (2 to less than 6 years of age) administered one-half the recommended adult dose (1 spray per nostril) of PATANASE Nasal Spray twice daily for a minimum of 14 days. The mean C_{max} and AUC_{0-12} of olopatadine were 13.4 ± 4.6 ng/mL and 75.0 ± 26.4 ng·hr/mL respectively. The mean C_{max} and AUC_{0-12} of olopatadine N-oxide and N-desmethyl olopatadine were similar to that of patients 6 to 11 years of age.

Drug Interaction Studies

Drug interactions with inhibitors of liver enzymes are not anticipated because olopatadine is eliminated predominantly by renal excretion. Olopatadine did not inhibit the *in vitro* metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Based on these data, drug interactions involving P450 inhibition are not expected. Due to the modest protein binding of olopatadine (55%), drug interactions through displacement from plasma proteins are also not expected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Olopatadine administered orally was not carcinogenic in mice and rats at doses of up to 500 mg/kg/day and 200 mg/kg/day, respectively (approximately 420 and 340 times the MRHD for adults and adolescents ≥ 12 years of age and 500 and 400 times the MRHD for children 6-11 years of age by intranasal administration on a mg/m^2 basis, respectively).

There was no evidence of genotoxicity when olopatadine was tested in an *in vitro* bacteria reverse mutation test (Ames), an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test.

Olopatadine administered orally to male and female rats at dose of 400 mg/kg/day, (approximately 680 times the MRHD for adults on a mg/m^2 basis) resulted in a decrease in the fertility index and reduced implantation rate. No effects on fertility were observed at dose of 50 mg/kg/day (approximately 85 times the MRHD for adults on a mg/m^2 basis).

13.2 Animal Toxicology

Reproductive Toxicology Studies

Olopatadine was not teratogenic in rabbits and rats at oral doses of up to 400 or 600 mg/kg/day, respectively (approximately 1,400 and 1,000 times the MRHD for adults on a mg/m^2 basis, respectively). However, a decrease in the number of live fetuses was observed in rabbits at the oral olopatadine doses of 25 mg/kg (approximately 88 times the MRHD for adults on a mg/m^2 basis) and above, and in rats at oral doses of 60 mg/kg (approximately 100 times the MRHD for adults on a mg/m^2 basis) and above. In rats, viability and body weights of pups were reduced on day 4 post partum at the oral doses of 60 mg/kg (approximately 100 times the MRHD for adults on a mg/m^2 basis) and above, but no effect on viability was observed at the dose of 20 mg/kg (approximately 35 times the MRHD for adults on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Seasonal Allergic Rhinitis

Adult and Adolescent Patients 12 Years of Age and Older:

The efficacy and safety of PATANASE Nasal Spray were evaluated in three randomized, double blind, parallel group, multicenter, placebo (vehicle nasal spray)-controlled clinical trials of 2 weeks duration in adult and adolescent patients, 12 years of age and older with symptoms of seasonal allergic rhinitis. The

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three clinical trials were conducted in the United States and included 1,598 patients (556 males, and 1,042 females) 12 years of age and older. In these three trials 587 patients were treated with PATANASE Nasal Spray 0.6%, 418 patients were treated with PATANASE Nasal Spray 0.4%, and 593 patients were treated with vehicle nasal spray. Assessment of efficacy was based on patient recording of 4 individual nasal symptoms (nasal congestion, rhinorrhea, itchy nose, and sneezing) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as reflective or instantaneous scores. Reflective scoring required patients to record symptom severity over the previous 12 hours; the instantaneous scoring required patients to record symptom severity at the time of recording. The primary efficacy endpoint was the difference from placebo in the percent change from baseline in the average of morning and evening reflective total nasal symptom score (rTNSS) averaged for the 2-week treatment period. In all 3 trials, patients treated with PATANASE Nasal Spray, two sprays per nostril, twice-daily, exhibited statistically significantly greater decreases in rTNSS compared to vehicle nasal spray. Results for the rTNSS from two representative trials are shown in Table 3.

Table 3: Mean Reflective Total Nasal Symptom Score (rTNSS) in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

	Treatment	N	Baseline	Change from Baseline	Difference from Placebo		
					Estimate	95% CI	p-value
Study 1	PATANASE Nasal Spray 0.6%	183	8.71	-3.63	-0.96	(-1.42, -0.51)	<0.0001
	PATANASE Nasal Spray 0.4%	188	8.90	-3.38	-0.71	(-1.17, -0.26)	0.0023
	Vehicle Nasal Spray	191	8.75	-2.67			
Study 2	PATANASE Nasal Spray 0.6%	220	9.17	-2.90	-0.98	(-1.37, -0.59)	<0.0001
	PATANASE Nasal Spray 0.4%	228	9.26	-2.63	-0.72	(-1.11, -0.33)	0.0003
	Vehicle Nasal Spray	223	9.07	-1.92			

In the 2-week seasonal allergy trials, onset of action was also evaluated by instantaneous TNSS assessments twice-daily after the first dose of study medication. In these trials, onset of action was seen after 1 day of dosing. Onset of action was evaluated in three environmental exposure unit studies with single doses of PATANASE Nasal Spray. In these studies, patients with seasonal allergic rhinitis were exposed to high levels of pollen in the environmental exposure unit and then treated with either PATANASE Nasal Spray or vehicle nasal spray, two sprays in each nostril, after which they self-reported their allergy symptoms hourly as instantaneous scores for the subsequent 12 hours. PATANASE Nasal Spray 0.6% was found to have an onset of action of 30 minutes after dosing in the environmental exposure unit.

Pediatric Patients 6 to 11 Years of Age:

There were 3 clinical trials of 2 weeks duration with olopatadine nasal spray in patients 6 to 11 years of age with seasonal allergic rhinitis. Efficacy of Patanase Nasal Spray was evaluated in 2 of the 3 trials. One of the 2 trials that showed efficacy was a randomized, double blind, parallel group, multicenter, placebo (vehicle nasal spray)-controlled clinical trial of 2 weeks duration including 1,188 children ages 6 to < 12 years with seasonal allergic rhinitis. Assessment of efficacy was based on patient/caregiver recording of 4 individual nasal symptoms (nasal congestion, rhinorrhea, itchy nose, and sneezing) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as reflective or instantaneous scores. Reflective scoring captured symptom severity over the previous 12 hours; the instantaneous scoring captured symptom severity at the time of recording. The primary efficacy endpoint was the difference from placebo in the percent change from baseline in the average of patient/caregiver-reported morning and evening reflective total nasal symptom score (rTNSS) averaged for the 2-week treatment period. Patients treated with PATANASE Nasal Spray, 1 or 2 sprays per nostril twice daily, had statistically significantly greater decreases in rTNSS compared to vehicle nasal spray. Results for rTNSS are shown in Table 4.

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Table 4: Mean Reflective Total Nasal Symptom Score (rTNSS) in Pediatric Patients 6-11 Years of Age with Seasonal Allergic Rhinitis

Treatment	N	Baseline	Change from Baseline	Difference from Placebo		
				Estimate	95% CI	p-value
PATANASE Nasal Spray 0.6%, 1 spray per nostril twice daily	294	8.99	-2.24	-0.55	(-0.90, -0.19)	0.0015
Vehicle Nasal Spray, 1 spray per nostril twice daily	294	9.09	-1.70			

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PATANASE Nasal Spray, 665 mcg is supplied in a white plastic bottle with a metered-dose manual spray pump, a white nasal applicator and a blue overcap in a box of 1 (NDC 0065-0332-30). Each trade size bottle contains 30.5 g of clear, colorless liquid and will provide 240 metered sprays. After priming [*see Dosage and Administration (2)*], each spray delivers a fine mist containing 665 mcg of olopatadine hydrochloride in 100 microliters of formulation through the nozzle.

Before initial use, prime PATANASE Nasal Spray by releasing 5 sprays or until a fine mist appears. After periods of non-use greater than 7 days, re-prime PATANASE Nasal Spray by releasing 2 sprays. The correct amount of medication cannot be assured before the initial priming and after 240 sprays have been used, even though the bottle is not completely empty. The nasal device should be discarded after 240 sprays (enough for 30 days of dosing) have been used.

Net content 30.5 g, 240 sprays: NDC 0065-0332-30 (trade size)

16.2 Storage

Store at 4° to 25° C (39° to 77° F). Rx Only.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling accompanying the product.

17.1 Local Nasal Effects and Other Common Adverse Reactions

Patients should be informed that treatment with PATANASE Nasal Spray may lead to adverse reactions, which include epistaxis and nasal ulcerations. [*see Warnings and Precautions (5.1)*] Other common adverse reactions reported with use of PATANASE Nasal Spray include bitter taste, headache, and pharyngolaryngeal pain, [*see Adverse Reactions (6)*].

17.2. Activities Requiring Mental Alertness

Somnolence has been reported in some patients taking PATANASE Nasal Spray. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as driving or operating machinery after administration of PATANASE Nasal Spray [*see Warnings and Precautions (5.2)*].

17.3 Concurrent Use of Alcohol and other Central Nervous System Depressants

Concurrent use of PATANASE Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur [*see Warnings and Precautions (5.2)*].

17.4. Keep Spray Out of Eyes

Patients should be informed to avoid spraying PATANASE Nasal Spray in their eyes.

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