AUSTRALIAN PRODUCT INFORMATION

AZEP® NASAL SPRAY

Azelastine hydrochloride Nasal Spray

1 NAME OF THE MEDICINE

Azelastine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation (0.137 mL) contains 137 µg azelastine hydrochloride (equivalent to 125 µg azelastine as the base).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

AZEP NASAL SPRAY is a clear, colourless, buffered, isotonic aqueous solution with a pH of 6.8.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the symptomatic treatment of seasonal allergic rhinitis and perennial allergic rhinitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children aged 5 years and over:

Each spray contains 125 µg of azelastine (as hydrochloride).

One spray into each nostril twice daily as necessary (equivalent to a daily dose of 0.50 mg azelastine (as hydrochloride)).

Long term treatment:

Azelastine nasal spray may be used until symptoms cease, but no longer than 6 months, uninterruptedly.

Instructions for handling:

The spray should be used with the head held upright, after first blowing the nose.

1. The protective cap should be removed.
2. Before the first use, the pump should be primed by spraying 2-3 times, until an even spray is produced.
3. One spray should be used in each nostril with the head tilted forward (looking at toes). Do not keep the head upright or tilted backwards.
4. Sniffing should only be slow and gentle.
5. The nozzle should be wiped and the protective cap replaced.

The pump should also be primed again after storage for 3 or more days.

4.3 CONTRAINDICATIONS

Hypersensitivity to any of the ingredients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in the elderly

A pharmacokinetic study in elderly patients (n=15) receiving oral azelastine hydrochloride 4.4 mg twice daily found a prolongation of the T_{max} and an increase in C_{max} and AUC compared to results in healthy volunteers. There have been no specific studies in the elderly with the nasal spray. In clinical and PMS studies of the nasal spray, no increase in the incidence of adverse reactions has been seen in elderly patients.

Use in renal impairment

In a single oral dose study in 9 patients, renal insufficiency (creatinine clearance <50 mL/min) resulted in a 70-75% higher C_{max} and AUC compared to normal subjects. However, the number of patients evaluated in this study is too small to draw meaningful conclusions. No information regarding the use of AZEP NASAL SPRAY in renally impaired patients is available.

Use in hepatic impairment

No significant difference was found in t½, C_{max} or AUC in an oral single dose study in 6 patients with hepatic impairment compared to normal subjects. Caution is warranted in extrapolating these data to long - term use.

Paediatric use

The efficacy and safety of AZEP NASAL SPRAY in children under 5 years of age has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific interactions have been studied with AZEP NASAL SPRAY. Interaction studies at high oral doses have been performed. However, they bear no relevance to azelastine nasal spray as systemic levels after administration of the nasal spray are in the nanogram range.

After oral administration of 4.4 mg azelastine hydrochloride twice daily, cimetidine has been shown to increase the plasma levels of azelastine. This is thought to be due to cimetidine inhibiting the metabolism of azelastine by interacting with the hepatic cytochrome P450 system. No interaction was seen following co-medication with ranitidine.

When given in combination, azelastine hydrochloride 4.4 mg tablets and alcohol showed sedative effects. As no specific information is available with the nasal spray, caution is required if AZEP NASAL SPRAY is used concomitantly with alcohol or other CNS depressants.

No significant pharmacokinetic interaction was observed with the co-administration of an oral 4.4 mg dose of azelastine hydrochloride twice daily and theophylline 300 mg or 400 mg twice daily.

Interaction studies investigating the cardiac repolarisation effects of concomitantly administered oral azelastine hydrochloride (4.4 mg b.d.) and erythromycin (500 mg t.i.d.) or ketoconazole (200 mg b.d.) were conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or OTC based on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement of azelastine plasma levels; however, no effects on QTC were observed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In male and female rats, azelastine at oral doses of 30 mg/kg/day and greater (resulting in plasma levels which were at least about 400 times above the plasma levels at the recommended therapeutic intranasal dose) caused a decrease in the fertility index, but in long term toxicity studies up to 2 years there were no drug-related alterations

in reproductive organs either in males or in females in this species. A clinical study in 21 healthy human females using an intranasal dose of 1.12 mg/day found no effect on ovulation or sexual hormone pattern.

Use in pregnancy (Category B3)

There are no adequate and well-controlled clinical studies in pregnant women. AZEP NASAL SPRAY should be used during pregnancy only if the benefit to the mother justifies the potential risk to the foetus.

In pregnant rats there was evidence of significant diapiacental transfer of the drug to the foetuses. Azelastine was embryo lethal and teratogenic in mice at oral doses greater than 30 mg/kg/day. In rats, azelastine was embryo-toxic at oral doses greater than 3 mg/kg/day, and teratogenicity and embryolethality were seen at doses greater than 30 mg/kg/day. In rabbits, azelastine was teratogenic at oral doses greater than 20 mg/kg/day. In pregnant rats, azelastine demonstrated no peri/postnatal toxicity at oral doses up to 30 mg/kg/day.

In rats, the no effect doses resulted in plasma levels which were at least about 25 times above the plasma levels at the recommended therapeutic intranasal dose in humans. (The calculation of the safety factor is based on plasma levels derived from oral subchronic toxicity studies).

Use in lactation

It is not known whether azelastine hydrochloride is excreted in human milk. No data are available in humans. Therefore, caution should be exercised when azelastine is administered to nursing women. Azelastine should not be used in lactating women unless the expected benefits outweigh the risks to the feeding infant.

In lactating rats, approximately 0.2% of a 10 mg/kg oral dose of 14C-azelastine was transferred to the maternal milk. A peri/postnatal study in rats showed no adverse effect at oral doses up to 30 mg/kg/day.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

In isolated cases, fatigue, weariness, exhaustion, dizziness or weakness, that may also be caused by the disease itself, may occur when using azelastine nasal spray. In these cases, the ability to drive and use machines may be impaired. Alcohol may enhance this effect.

Somnolence was uncommon in clinical trials and post-marketing surveillance studies, occurring with a similar incidence to placebo in clinical trials using the nasal spray in the recommended dosage. Patients should be advised to assess their individual responses to AZEP NASAL SPRAY before engaging in any activity requiring mental alertness, such as driving a car or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Azelastine nasal spray is generally well-tolerated. The most frequent complaints with the recommended dose (one spray per nostril twice daily) reported in clinical trials and in the post-marketing program were: mild, transient inflammation of the nasal mucosa (e.g. stinging, itching, sneezing and epistaxis), the experience of nose bleeding, and the occurrence of a substance-specific bitter taste, which may lead to nausea. The experience of the bitter taste may be due to incorrect administration such as tilting the head backwards too far.

Clinical Trial Data

The following table shows adverse events reported in clinical trials with azelastine nasal spray with an incidence of >1%, irrespective of a causal relationship to the administration of the drug.

Table 1: Adverse events reported in clinical trials

Preferred term	Azelastine (0.56mg/day) (n=1890)	Placebo (n=585)
Respiratory		
Epistaxis	2.2	6.0
Pharyngitis	3.2	2.9
Rhinitis	4.2	6.3
Coughing	1.5	3.6
Upper RTI	0.6	2.6
Asthma	0.5	2.1
Bronchitis	1.2	0.5
Gastro-intestinal		
Dyspepsia	1.1	0.7
Nausea	1.4	0.5
Dry mouth	0.3	1.4
Neurological		
Headache	4.6	8.2
Other		
Taste perversion	4.5	0.9
Application Site reaction	3.9	3.6
Influenza-like symptoms	2.2	3.8
Fatigue	1.7	0.5

Post-Marketing Data

The following adverse reactions were reported with a frequency of ≥ 0.05% in Post-Marketing Surveillance studies in a total of 12,221 patients.

Common:	≥ 1/100 and < 1/10 (≥1% and <10%)
Uncommon:	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%)
Rare:	≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)

Table 2: Adverse events reported in Post-Marketing Surveillance studies

	Preferred Term
Respiratory	
Common	Rhinitis
Uncommon	Epistaxis

Rare	Pharyngitis, Coughing
Gastro-intestinal	
Uncommon	Dry mouth, Nausea, Stomatitis
Neurological	
Uncommon	Headache, Somnolence
Rare	Nervousness
Other	
Common	Taste perversion
Uncommon	Application site reaction, Fatigue
Rare	Taste loss

The following adverse effects have also been observed: hypersensitivity dizziness, weakness, rash, pruritus, urticaria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

With the nasal route of administration overdosage reactions are not anticipated. To date, there has been only one report of incorrect usage: a 2 year old boy drank approximately 10 mL of azelastine nasal spray. This led to a burning sensation in the nose and mouth and to spontaneous vomiting, these events lasting 5 - 10 minutes. Pulse rate, blood pressure and respiration were normal and stable, and a normal pupil reaction was found. No tissue damage in the mouth or throat occurred. The boy recovered completely.

In the event of overdosage after accidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) are to be expected based on the results of animal experiments. Symptomatic and supportive treatment should be instigated as there is no known antidote.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Azelastine hydrochloride, a phthalazinone derivative, is a potent antiallergic compound with histamine H1-receptor antagonist activity and a rapid onset and long duration of action. The major metabolite, desmethylazelastine, also exhibits H1-receptor antagonist activity. AZEP NASAL SPRAY is administered as a racemic mixture. The racemate, R- and S- enantiomers were equally potent at inhibiting eyelid histamine-induced oedema in rats, however the R-enantiomer was 2-fold less active at inhibiting eyeball histamine-induced oedema.

Data from *in vivo* (preclinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions, e.g. histamine, leukotrienes, PAF and serotonin.

In experimental studies in humans, AZEP NASAL SPRAY was effective in the prophylaxis of histamine- and allergen-induced nasal symptoms. The effect appears within 15 minutes of drug application and lasts for up to 12 hours. AZEP NASAL SPRAY also has an effect on the inflammatory process of allergy as defined by a significant decrease in the eosinophilic and neutrophilic infiltration, and ICAM-1 expression during both early and late phase reactions following allergen challenge.

Clinical Trials

In a number of placebo- and active-controlled clinical studies, AZEP NASAL SPRAY has been shown to be effective in the symptomatic treatment of allergic rhinitis, especially for sneezing, itchy nose, rhinorrohoea and nasal blockage. Studies in seasonal allergic rhinitis were generally conducted over 2-6 weeks; in perennial allergic rhinitis, controlled studies were conducted over 6 weeks, and two open long term studies were conducted over a 6 month period.

Seasonal allergic rhinitis: Two randomised, double-blind trials (n=162, n=100) in adults aged 16-65 years showed that azelastine nasal spray 0.14 mg/nostril b.d. had equivalent efficacy to oral terfenadine 60 mg b.d. over 6 weeks. The primary efficacy measure was reduction in the rhinitis score. In one of these trials, nasal rhinometry was also performed with azelastine therapy and shown to significantly reduce nasal airways resistance over a six week period. A further randomised, double-blind, placebo-controlled trial (n=83) assessed the efficacy for 2 weeks in children aged 5 - 12 years. Response was defined as at least a 50% improvement in a nasal score of sneezing, pruritus and rhinorrohoea within 3 days of starting treatment. The response rate was 52.5% in the azelastine group and 41.9% in the placebo group (p=0.38). With regard to the nasal symptoms sneezing, nasal irritation and rhinorrohoea, the mean score was significantly decreased by Day 3 compared to placebo (p=0.039).

Perennial allergic rhinitis: A randomised, double-blind trial in adults aged 18 - 49 years found that azelastine nasal spray 0.14 mg/nostril b.d. was equivalent in efficacy to oral terfenadine 60mg bd over 6 weeks. Of the 52 patients enrolled, 22 were evaluable in the azelastine group and 26 in the terfenadine group. A randomised open trial in adults aged 18 - 65 years found azelastine nasal spray 0.14mg/nostril b.d. to be equivalent in efficacy to budesonide spray 0.05 mg/nostril b.d. for 6 weeks. Of the 193 patients enrolled, 92 were evaluable in the azelastine group and 89 in the budesonide group Equivalent efficacy was based on symptomatology, nasal airflow resistance and resolution of nasal hyperplasia.

Two randomised, double-blind, placebo-controlled trials assessed the efficacy of azelastine 0.14 mg/nostril b.d. for 6 weeks in children aged 5 - 12 years. In one trial, azelastine was significantly better than placebo in improving sneezing, nasal blockage, nasal itch and rhinorrohoea measured on a visual analogue scale. Of the 125 patients enrolled, 60 were evaluable in each group. In the other trial, which experienced poor compliance, there was no significant difference between the treatment groups. Of 162 patients enrolled, 72 were evaluable in the azelastine group and 71 in the placebo group. In a 2 week, single-blind trial (n=45) in children aged 5-18 years, budesonide aqueous suspension 0.2 mg/day was superior to azelastine 0.56 mg/day.

Long term studies: Six and 12 months uncontrolled trials (n=185, n=36) in adults aged 17 - 65 years provide maintenance of long term efficacy data in perennial allergic rhinitis and demonstrate efficacy for up to 12 month. A further trial (n=62) found a significant reduction in nasal symptom score over 6 months and was supportive of long-term efficacy in children aged 7 - 16 years.

Other information

There were no findings on nasal examination in an 8 week study that suggested any adverse effects on the nasal mucosa.

In a double-blind, placebo-controlled, parallel group study, 69 patients with perennial allergic rhinitis were randomised to receive azelastine and 36 to placebo, to evaluate the safety and tolerability of AZEP NASAL SPRAY following administration of 2 sprays per nostril (1.12 mg/day) for 8 weeks. A 12-lead ECG was performed at baseline and after 8 weeks of treatment, 2 - 4 hours after dosing. There was no evidence of an effect of AZEP

NASAL SPRAY on cardiac repolarisation as represented by the QTC interval of the ECG. The results from this study thus support the cardiac safety of AZEP NASAL SPRAY.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The systemic bioavailability of azelastine nasal spray has not been directly measured. In healthy volunteers, using cross-trial data, bioavailability is estimated at 20%. In patients with allergic rhinitis, again using cross-trial data, bioavailability is estimated at 40 – 60%.

Distribution

After oral and intravenous administration, the mean volume of distribution was 14.5 L/kg and mean terminal half-life was 22 h.

In patients receiving a total daily dose of 0.56 mg azelastine hydrochloride (given as two sprays per nostril once daily), the steady state mean plasma concentrations of azelastine observed two hours after dose were about 0.65 ng/mL. A doubling of the total daily dose to 1.12 mg azelastine hydrochloride (two sprays per nostril twice daily) resulted in steady state mean plasma concentrations of azelastine of 1.09 ng/mL, suggesting dose proportionality within the dose range.

In vitro studies with human plasma indicate that the plasma protein binding of azelastine and desmethylazelastine are approximately 88% and 97% respectively.

Metabolism

Azelastine is extensively metabolised, desmethylazelastine being the principal metabolite. No specific isoform of cytochrome P450 was found to be specific in the metabolism of azelastine at low concentrations (6 - 30 ng/mL) in human liver microsomes.

Excretion

The mean terminal half-life of desmethylazelastine was 56 h. Up to 74% of a radiolabelled oral or intravenous dose is excreted in faeces and 26% in urine. Thirteen per cent is excreted in urine as unchanged azelastine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Azelastine demonstrated no genotoxic potential in standard assays for gene mutations, chromosomal damage and DNA damage.

Carcinogenicity

Azelastine demonstrated no carcinogenic potential in mice and rats at dietary doses up to 25 and 30 mg/kg/day respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- hypromellose
- disodium edetate
- citric acid
- dibasic sodium phosphate dodecahydrate

- sodium chloride
- purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

AZEP NASAL SPRAY 5 mL: store below 25°C (Do not refrigerate).

AZEP NASAL SPRAY 20 mL: store below 30°C (Do not refrigerate).

6.5 NATURE AND CONTENTS OF CONTAINER

AZEP NASAL SPRAY is available in a 5 mL and 20 mL amber glass bottle with fitted valve assembly.

Australian Register of Therapeutic Goods (ARTG)

AUST R 104853 – AZEP NASAL SPRAY azelastine 125µg/actuation (as hydrochloride) nasal spray aerosol, pump actuated-metered dose

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

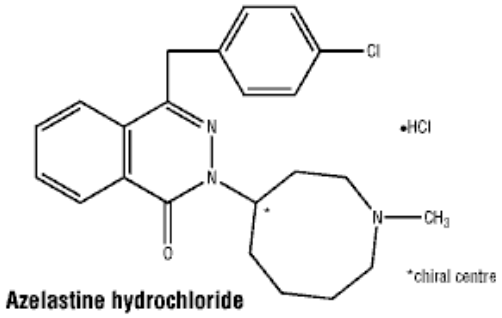
6.7 PHYSICOCHEMICAL PROPERTIES

Azelastine hydrochloride is a white to light beige crystalline, odourless powder. It is freely soluble in chloroform, soluble in ethanol and sparingly soluble in water. It is practically insoluble in ether, n-hexane and toluene.

Chemical Structure

Azelastine hydrochloride is chemically D,L-4-(p-ChlorobenzyI)-2-(Nmethylperhydroazepinyl)-(4) 1(2H)-phthalazinone hydrochloride.

It has the following structural formula:



Azelastine hydrochloride

The chemical formula is $C_{22}H_{24}OCIN_3$.HCI and its molecular weight is 418.37. It is presented as the racemate.

CAS number

79307-930

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 (Pharmacy Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

21/07/2004

10 DATE OF REVISION

09/12/2021

Summary table of changes

Section changed	Summary of new information
All	Minor editorial changes
6.4	Update storage conditions