DESCRIPTION

1. Composition
   Tablets 0.5 mg:
   Each white, sugar coated tablet contains 0.5 mg of azelastine hydrochloride.
   It also contains powdered acacia, carnauba wax, hydrated silicon dioxide, microcrystalline cellulose, titanium oxide, stearic acid, calcium stearate, sucrose, talc, precipitated calcium carbonate, corn starch, lactose hydrate, white shellac, hydroxypropylcellulose, povidone and macrogol 6000 as inactive ingredients.

   Tablets 1 mg:
   Each white, sugar coated tablet contains 1 mg of azelastine hydrochloride.
   It also contains carnauba wax, hydrated silicon dioxide, microcrystalline cellulose, titanium oxide, stearic acid, calcium stearate, sucrose, talc, precipitated calcium carbonate, corn starch, lactose hydrate, white shellac, hydroxypropylcellulose, pullulan, povidone and macrogol 6000 as inactive ingredients.

2. Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dosage form and identification code</th>
<th>Appearance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azeptin Tablets 0.5mg</td>
<td>Sugar-coated tablets €232</td>
<td>Diameter (mm) 6.2 Weight (mg) 100 Thickness (mm) 3.5</td>
<td>White</td>
</tr>
<tr>
<td>Azeptin Tablets 1mg</td>
<td>Sugar-coated tablets €233</td>
<td>Diameter (mm) 6.7 Weight (mg) 120 Thickness (mm) 3.5</td>
<td>White</td>
</tr>
</tbody>
</table>

INDICATIONS
Bronchial asthma
Allergic rhinitis

DOSAGE AND ADMINISTRATION

1. Bronchial asthma
   The usual adult dosage for oral use is 2 mg of azelastine hydrochloride twice a day after breakfast and at bedtime. The dosage may be adjusted depending on the patient’s age and symptoms.

2. Allergic rhinitis, urticaria, eczema/dermatitis, atopic dermatitis, pruritus and prurigo
   The usual adult dosage for oral use is 1 mg of azelastine hydrochloride twice a day after breakfast and at bedtime. The dosage may be adjusted depending on the patient’s age and symptoms.

PRECAUTIONS

1. Important Precautions
   (1) Since Azeptin may induce drowsiness, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.
   (2) When a steroid is to be tapered off in a patient undergoing long-term steroid therapy, after initiation of Azeptin, the steroid dosage should be reduced slowly under close supervision.
   (3) If Azeptin is administered to patients with bronchial asthma, it should be explained to them that Azeptin is not a drug that rapidly relieves asthma attacks.
   (4) It is recommended that patients with seasonal allergic diseases be started on Azeptin immediately before the beginning of the unfavorable season and that the administration be continued until after its end.

2. Adverse Reactions
   Adverse reactions were reported in 439 of 14,365 patients. (At the end of the reexamination period)
Psychoneurologic

Sleepiness and malaise
Dizziness, headache and numbness of limbs
Incidence unknown

Gastrointestinal

Thirst and nausea/vomiting
Oral and perioral roughness, anorexia, heart burn, stomach discomfort, abdominal pain, constipation and diarrhea

Cardiovascular

Facial hot flushes and palpitations

Respiratory

Nasal dryness and respiratory distress

Hepatic

Elevation of AST (GOT) and ALT (GPT), etc.
Elevation of Al-P

Hypersensitivity

Rash

Hematologic

Leucocytosis

Urinary

Pollakiuria

Others

Bitter taste and taste disorder
Edema
Menstrual disorder

Note: In the event of such symptoms, treatment should be discontinued.

3. Use in the Elderly

Since the elderly often have a physiological hypofunction, it is advisable to take measures, such as reduction in dosage, under careful supervision.

4. Use during Pregnancy, Delivery or Lactation

(1) AZEPTIN should only be used in pregnant women or women suspected of being pregnant if the expected therapeutic benefits outweigh the possible risk of treatment.

[AZEPTIN has been reported to be potentially teratogenic at large doses (greater than 370 times the recommended clinical dose) in an animal study (in rats).

(2) It is advisable to avoid administration to nursing mothers. When AZEPTIN must be used, breast feeding should be discontinued during treatment.

[It has been reported that AZEPTIN is excreted in breast milk in an animal study (in rats).]

5. Pediatric Use

Safety in low birth weight infants, neonates, nursing infants and infants has not been established (insufficient clinical experience).

6. Precautions concerning Use

Caution in handing over drug

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

7. Other Precautions

Because of the bitterness of the drug itself, a bitter taste and taste disorder may be experienced.

PHARMACOKINETICS

1. Blood concentration

When AZEPTIN was administered orally to healthy male adult volunteers at a single dose of 1 mg (4 men), 2 mg (4 men), 3 mg (4 men), 3 mg (6 men) and 4 mg (4 men), the peak plasma concentrations were 0.6, 1.1, 2.0 and 2.1 ng/mL, respectively. The times to reach the peak plasma concentration were 4 hr after administration of 1 to 3 mg and 6 hr after administration of 4 mg.

When AZEPTIN was repeatedly administered orally to 6 healthy male adult volunteers at dose of 3 mg twice a day, the plasma concentration reached a steady state within 6 days and the biological half-life was found to be about 16.5 hr.

CLINICAL STUDIES

Clinical efficacy

The efficacy rate ("remarkably effective+effective") was 31.2% (138/443 patients) for bronchial asthma. It increased 66.4% (294/443 patients) when fairly to remarkably effective was taken into account.\(^1\)

The efficacy rate ("remarkably effective+effective") was 49.8% (309/620 patients) for allergic rhinitis. It increased 80.2% (497/620 patients) when fairly to remarkably effective was taken into account.\(^2,3\)
The efficacy rate ("remarkably effective+effective") was 64.5% (142/220 patients) for dermatoses (urticaria, eczema/dermatitis, atopic dermatitis, pruritus cutaneous and prurigo). It increased 83.2% (183/220 patients) when fairly to remarkably effective was taken into account. The usefulness of AZEPTIN has been established in double blind clinical trials.

PHARMACOLOGY

1. Mechanisms of Action

(1) Inhibition of the production and release of leukotrienes and antagonism to leukotrienes

Azelastine hydrochloride inhibits the production and release of leukotrienes C4, D4 and B4 in guinea pig lung sections and human neutrophils and eosinophils. Its inhibitory action is considered to reside in its ability to inhibit calcium ion influx into the cell, inhibit 5-lipoxygenase activity, increase intracellular cyclic AMP and stabilize the cell membrane, etc. Azelastine hydrochloride has also been shown to inhibit the contraction of isolated guinea pig ileum and bronchial muscle induced by leukotrienes C4 and D4, and the migration of neutrophils induced by leukotriene B4.6-9)

(2) Inhibition of histamine release and antagonism to histamine

Azelastine hydrochloride inhibits histamine release from human and rabbit basophils, and rat mast cells, and exhibits an antihistaminic action in the contraction reaction of guinea pig bronchial muscle and ileum.9-14)

(3) Inhibition of the migration and infiltration of inflammatory cells and production of active oxygen

Azelastine hydrochloride inhibits the migration of human neutrophils induced by leukotriene B4, and the migration and infiltration of guinea pig eosinophils induced by PAF. Azelastine hydrochloride also exhibits a marked inhibitory effect on the production of active oxygen in guinea pig neutrophils.8,15,16)

2. Inhibition of experimental allergic reactions

Azelastine hydrochloride inhibits the following over a long period of time at low oral doses: passive cutaneous anaphylactic reactions (PCA) in guinea pigs and rats, experimental asthma in guinea pigs due to the inhalation of leukotriens, PAF and histamine, experimental allergy rhinitis in dogs and Arthus reaction (type III allergy reaction) in guinea pigs.17-19)

3. Reduction of hypersensitivity in airways and nasal mucosa

It has been demonstrated in airways and nasal mucosal hypersensitivity tests that azelastine hydrochloride reduces airway and nasal mucosal hypersensitivity in patients with asthma or allergic rhinitis.20,21)

PHYSICOCHEMISTRY

Nonproprietary name: Azelastine Hydrochloride

Chemical name:

4-[(4-Chlorophenyl)methyl]-2-[(4RS)-(1-methylazepan-4-y1)]phthalazin –1(2H)-one monohydrochloride

Molecular formula: C22H24ClN3O · HCl

Molecular weight: 418.36

Structural formula:

<table>
<thead>
<tr>
<th>N</th>
<th>O</th>
<th>Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>N</td>
<td>CH3</td>
</tr>
</tbody>
</table>

And enantiomer

Description:

Azelastine hydrochloride occurs as a white crystalline powder. It is soluble in formic acid, slightly soluble in water and in ethanol (99.5).

Azelastine hydrochloride shows no optical rotation.

Melting point: about 225°C (decomposition)

PACKAGING

AZEPTIN Tablets 0.5 mg:

Boxes of 100 and 500 in press-through packages

AZEPTIN Tablets 1 mg:

Boxes of 100, 280 (28 Tabs. × 10), 500, 1,000, 1,400 (28Tabs. × 50) and 3,000 tablets in press-through packages, and bottles of 500

REFERENCES


REQUEST FOR LITERATURE SHOULD BE MADE TO:
Safety Management Department
Fax: 03-3811-2710
Eisai Co., Ltd.

REQUEST FOR PRODUCT INFORMATION SHOULD BE MADE TO:
Customer Information Service
Free Dial: 0120-419-497
Eisai Co., Ltd.

Manufactured and marketed by:
Eisai Co., Ltd.
6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088