

The content of this leaflet was approved by the Ministry of Health in February 2015 and updated according to the guidelines of Ministry of Health in May 2019.

MIZOLLEN TABLETS
SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of The Medicinal Product

MIZOLLEN tablets 10 mg, film-coated tablets

2. Qualitative and Quantitative Composition

Mizolastine 10mg per tablet.

Excipients with known effect:

Lactose monohydrate (125mg/tablet)

Hydrogenated castor oil (25mg/tablet)

Propylene glycol (0.45mg/tablet)

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Modified-release tablet.

Oblong, white tablets with a scored line on one side and a mark "MZI 10" on the reverse side.

4. Clinical Particulars

4.1 Therapeutic indications

Mizolastine is a long acting H1- antihistamine indicated for the symptomatic –treatment –of seasonal allergic rhinoconjunctivitis (hay fever), perennial allergic rhinoconjunctivitis and urticaria.

4.2 Posology and method of administration

Adults, including the elderly, and children 12 years of age and over:

The recommended daily dose is one 10mg tablet

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant administration with macrolide antibiotics or systemic imidazole antifungals.
- Significantly impaired hepatic function.
- Clinically significant cardiac disease or a history of symptomatic arrhythmias.
- Patients with known or suspected QT prolongation or with electrolyte imbalance, in particular hypokalaemia.
- Clinically significant bradycardia.
- Medicinal products known to prolong the QT interval, such as Class I and III anti-arrhythmics.

4.4 Special warnings and precautions for use

Mizolastine has a weak potential to prolong the QT interval in a few individuals. The degree of prolongation is modest and has not been associated with cardiac arrhythmias.

The elderly may be particularly susceptible to the sedative effects of mizolastine and the potential effects of the medicinal product on cardiac repolarisation.

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Mizolastine contains hydrogenated castor oil which can cause stomach upset and diarrhoea.

4.5 Interactions with other medicinal products and other forms of Interaction

Although the bioavailability of mizolastine is high and the medicinal product is principally metabolised by glucuronidation, systemically administered ketoconazole and erythromycin moderately increase the plasma concentration of mizolastine and their concurrent use is contraindicated.

Concurrent use of other potent inhibitors or substrates of hepatic oxidation (cytochrome P450 3A4) with mizolastine should be approached with caution. These would include cimetidine, ciclosporin, and nifedipine.

Alcohol: In studies with mizolastine, no potentiation of the sedation and the alteration in performance caused by alcohol has been observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of mizolastine for use in human pregnancy has not been established. The evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and post-natal development. However, as with all medicinal products, mizolastine should be avoided in pregnancy, particularly during the first trimester.

Breast feeding

Mizolastine is excreted into breast milk, therefore its use by lactating women is not recommended.

4.7 Effects on ability to drive and use machines

Most patients taking mizolastine may drive or perform tasks requiring concentration. However, in order to identify sensitive people who have unusual reactions to medicinal products, it is advisable to check the individual response before driving or performing complicated tasks.

4.8 Undesirable effects

Gastro-intestinal disorders:

Common: dry mouth, diarrhoea, abdominal pain (including dyspepsia), nausea.

Not known: vomiting.

Central nervous system disorders and psychiatric disorders:

Common: drowsiness often transient, headache, dizziness,

Uncommon: anxiety and depression.

Liver disorders:

Uncommon: raised liver enzymes.

Hematological disorders:

Very rare: low neutrophil count.

Body as a whole:

Common: asthenia often transient, increased appetite associated with weight gain.

Very rare: allergic reactions including anaphylaxis, angioedema, generalized rash/urticaria, pruritus and hypotension.

Cardiovascular disorders:

Uncommon: hypotension, tachycardia, palpitations.

Very rare: vasovagal attack

Musculoskeletal disorders:

Uncommon: arthralgia and myalgia.

Description of selected adverse reactions

There were reports of bronchospasm and aggravation of asthma but in view of the high frequency of asthma in the patient population being treated, a causal relationship remains uncertain.

Treatment with certain antihistamines has been associated with QT interval prolongation increasing the risk of serious cardiac arrhythmias in susceptible subjects.

Minor changes in blood sugar and electrolytes have been observed rarely. The clinical significance of these changes in otherwise healthy individuals remains unclear. Patients at risk (diabetics, those susceptible to electrolyte imbalance and cardiac arrhythmias) should be monitored periodically.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

4.9 Overdose

In cases of overdose, general symptomatic surveillance with cardiac monitoring including QT interval and cardiac rhythm for at least 24 hours is recommended, along with standard measures to remove any unabsorbed medicinal product.

Studies in patients with renal insufficiency suggest that haemodialysis does not increase clearance of the medicinal product.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Antihistamines for systemic use (ATC code: R06AX25)

Mechanism of action

Mizolastine possesses antihistamine and antiallergic properties due to a specific and selective antagonism of peripheral histamine H₁ receptors. It has also been shown to inhibit histamine release from mast cells (at 0.3 mg/kg orally) and the migration of neutrophils (at 3 mg/kg orally) in animal models of allergic reactions.

Clinical efficacy and safety

In man, histamine-induced wheal and flare studies have shown that mizolastine 10 mg is a rapid, potent (80 % inhibition after 4 hrs) and sustained (24hr) antihistamine. No tachyphylaxis occurred after long-term administration.

In both preclinical and clinical studies, no anticholinergic effect has been demonstrated.

5.2 Pharmacokinetic properties

Following oral administration mizolastine is rapidly absorbed. Peak plasma concentration is reached at a median time of 1.5 hours.

Bioavailability is 65% and linear kinetics have been demonstrated.

The mean elimination half-life is 13.0 hours with plasma protein binding of 98.4%.

In hepatic insufficiency the absorption of mizolastine is slower and the distribution phase longer, with a resulting moderate increase in AUC of 50%.

The principal metabolic pathway is glucuronidation of the parent compound. The cytochrome P₄₅₀ 3A4 enzyme system is involved in one of the additional metabolic pathways with formation of the hydroxylated metabolites of mizolastine. None of the identified metabolites contribute to the pharmacological activity of mizolastine.

An increase in mizolastine plasma levels, observed with systemic ketoconazole and erythromycin, led to concentrations equivalent to those obtained after a 15 to 20 mg dose of mizolastine alone.

In studies carried out in healthy volunteers, no clinically significant interaction has been recorded with food, warfarin, digoxin, theophylline, lorazepam, or diltiazem.

5.3 Preclinical safety data

Pharmacological studies in several species have shown an effect on cardiac repolarisation at doses in excess of 10-20 times the therapeutic dose. In conscious dogs, mizolastine has shown pharmacological interactions with ketoconazole at the electrocardiographic level at 70 times the therapeutic dose.

6. Pharmaceutical Particulars

6.1 List of excipients

Core: lactose monohydrate, hydrogenated castor oil, microcrystalline cellulose, tartaric acid, povidone, magnesium stearate, anhydrous colloidal silica, purified water.

Film-coating: hypromellose, titanium dioxide (E171), propylene glycol, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/(oPA/Aluminum/PVC) blisters: Pack of 15 tablets.

6.6 Special precautions for disposal

Tablets should not be taken if they become discoloured.

7. Marketing Authorization Holder

Sanofi-aventis Israel Ltd., 10 Beni Gaon, P.O.B. 8090, Netanya, 4250499, Israel

8. Manufacturer

Sanofi Winthrop Industrie, France

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