MIZOLLEN TABLETS

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of The Drug
MIZOLLEN tablets 10 mg, modified-release, film-coated tablet

2. Qualitative and Quantitative Composition
Mizolastine 10mg per tablet. For a 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 ingredient or to any of the excipients.
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.
Drugs 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 drug on cardiac repolarisation.
Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other Medicaments and other forms of Interaction
Although the bioavailability of mizolastine is high and the drug 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 Pregnancy and Lactation
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 drugs, mizolastine should be avoided in pregnancy, particularly during the first trimester. 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 drugs, it is advisable to check the individual response before driving or performing complicated tasks.

4.8 Undesirable Effects

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

Central nervous system 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, generalised rash/urticaria, pruritus and hypotension.

Cardiovascular disorders:
Uncommon: hypotension, tachycardia, palpitations,
Very rare: Vasovagal attack

Muscle and skeletal disorders:
Uncommon: arthralgia and myalgia.

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.

Due to the presence of castor oil, gastrointestinal disorders (nausea, vomiting, abdominal pain) may occur.

4.9 Overdose

In cases of overdosage, 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 drug. Studies in patients with renal insufficiency suggest that haemodialysis does not increase clearance of the drug.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Antihistamines for systemic use (ATC code : R06AX25)
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.
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 Pre-clinical 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: hydrogenated castor oil, lactose monohydrate, microcrystalline cellulose, tartaric acid, povidone, anhydrous colloidal silica, magnesium stearate, purified water.
Film-coating: hypromellose, titanium dioxide (E171), propylene glycol, purified water.

6.2 **Incompatibilities**
Not relevant.

6.3 **Special precautions for storage**
Do not store above 25°C. Store in a dry place in original packaging.

6.4 **Instructions for use and handling**
Do not use any tablets if their color has changed.

7. **Marketing Authorization Holder**
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8. **Manufacturer**
Sanofi Winthrop Industrie, France