

Mizollen 10 mg tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of The Drug

MIZOLLEN 10 mg, modified-release, film-coated tablet

2. Qualitative and Quantitative Composition

Mizolastine (I.N.N.) 10.00 mg per film-coated tablet

For the excipients, see section 6.1.

3. Pharmaceutical Form

Modified-release, film-coated tablet.

White, oblong tablet with a median line on one surface and "MZI 10" engraved on the opposite surface.

4. Clinical Particulars

4.1 Therapeutic Indications

Symptomatic treatment of seasonal allergic rhino-conjunctivitis (hay fever), perennial allergic rhino-conjunctivitis and urticaria.

4.2 Posology and Method of Administration

Oral route.

Adults, including the elderly, and children over 12 years old.

The recommended daily dose is one 10 mg tablet.

4.3 Contraindications

Hypersensitivity to the active substance or any of the other ingredients.

Concomitant treatment with macrolide antibiotics or systemic antifungals of the imidazole type.

Concomitant treatment with a drug known to prolong the QT interval, such as class I and III anti-arrhythmics.

Significant impairment of liver function.

Clinically significant heart disease, or history of symptomatic rhythm disorders.

Patients with known or suspected prolongation of the QT interval or with electrolyte imbalance, in particular hypokalemia.

Clinically significant bradycardia.



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4.4 Special Warnings and Precautions for Use

Mizolastine has a low potential to prolong the QT interval, only observed in a few cases. The degree of prolongation is slight and is not associated with cardiac dysrhythmia. Elderly patients may be particularly sensitive to the sedative effects of mizolastine and its potential effects on cardiac repolarization.

4.5 Interactions with other Medicaments and other forms of Interaction

Although the bioavailability of mizolastine is high and the drug is metabolized by glucuronide conjugation, systemically administered ketoconazole and erythromycin moderately increase the plasma concentration of mizolastine; therefore it is **contraindicated** to use these drugs with mizolastine. Precautions must be taken when combining mizolastine with other inhibitors or potent substrates of hepatic oxydation (cytochrome P450 3A4). These substances include cimetidine, cyclosporin and nifedipine.

Alcohol: studies performed with mizolastine have revealed no alcohol-induced potentiation of sedation or of impaired performance.

4.6 Pregnancy and Lactation

It has not yet been established whether it is safe to use mizolastine in pregnant women. The results of animal studies do not reveal any direct or indirect harmful effects on the development of the embryo or the fetus, the course of gestation, and peri-natal and post-natal development. However, as a precautionary measure, administration of mizolastine should be avoided during pregnancy, particularly during the first trimester.

Mizolastine is excreted into breast milk, and is not recommended to breast-feeding women.

4.7 Effects on Ability to Drive and Use Machines

Most patients treated with mizolastine may drive a vehicle or perform tasks requiring concentration. However, in order to identify sensitive individuals who could have unusual reactions to drugs, it is advisable to check individual response before driving a vehicle or performing complex tasks.

4.8 Undesirable Effects

Gastrointestinal disorders:

Frequent: diarrhea, abdominal pain (including dyspepsia), dry mouth, nausea.

Central nervous system and psychiatric disorders :

Frequent: drowsiness, often transient, headache, dizziness,

Rare: anxiety and depression.



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Hepatic disorders:

Rare: increase in liver enzymes.

Hematological disorders:

Very rare: neutropenia.

General effects:

Frequent: asthenia, often transient, increase in appetite accompanied by weight gain.

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

Cardiovascular disorders:

Rare: hypotension, tachycardia, palpitations,

Very rare: vagal malaise that may progress to syncope.

Muscle and skeletal disorders:

Very rare: arthralgia and myalgia.

Cases of bronchospasm and aggravation of asthma have been reported but, in view of the high frequency of asthma in the treated population, the causal relationship remains uncertain.

A prolongation of the QT interval has been observed in the course of treatment with certain antihistamines, increasing the risk of severe cardiac arrhythmia in patients at risk.

Minor variations in blood sugar levels and electrolytes have been observed in rare cases. The clinical relevance of these changes in otherwise healthy individuals remains uncertain. Patients at risk should be monitored periodically (especially in the event of diabetes, patients at risk of electrolyte imbalance or cardiac dysrhythmia).

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

4.9 Overdose

In the event of overdose, general symptomatic surveillance together with cardiac monitoring, including QT interval and cardiac rhythm for at least 24 hours is recommended along with standard measures to eliminate any unabsorbed substance. Studies conducted in patients with renal impairment suggest that hemodialysis does not increase mizolastine clearance.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic class: ANTIHISTAMINES FOR SYSTEMIC USE

ATC code: R06AX25



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Mizolastine has anti-allergic and antihistamine properties due to specific and selective blockade of peripheral histamine H1 receptors. It has also been demonstrated that mizolastine inhibits histamine release from the mastocytes (at a dose of 0.3 mg/kg per os) and the migration of neutrophils (at a dose of 3 mg/kg per os) in animal models of allergic reactions.

In man, studies of the erythematopapular reaction induced by histamine reveals that mizolastine 10 mg is a rapid and potent antihistamine (inhibition of 80% after 4 hours) with a long action duration (24 hours). No tachyphylaxis has been observed following long-term treatment.

Preclinical and clinical studies have revealed no anticholinergic effect.

5.2 Pharmacokinetic Properties

Mizolastine is absorbed rapidly following oral administration. The peak plasma concentration appears after a median period of 1.5 hours.

There is 65% bioavailability and pharmacokinetics are linear.

The mean elimination half-life is 13.0 hours, with 98.4% binding to plasma proteins.

Hepatic insufficiency slows mizolastine absorption and prolongs the distribution phase, resulting in a moderate increase in AUC (50%).

The principal metabolic pathway is glucuronide conjugation of the parent molecule. The cytochrome P450 3A4 enzymatic system is involved in one of the other metabolic pathways, with formation of the hydroxylated metabolites of mizolastine. None of the identified metabolites contribute to the pharmacological activity of mizolastine.

The increase in plasma levels of mizolastine observed in the event of concomitant administration of ketoconazole or erythromycin by systemic route reached values equivalent to those obtained following a dose of 15 to 20 mg of mizolastine alone.

In studies conducted in healthy volunteers, no clinically significant interaction with food, warfarin, digoxin, theophylline, lorazepam or diltiazem was observed.

5.3 Pre-clinical Safety Data

Pharmacological studies in several species have demonstrated an effect on cardiac repolarization at doses 10 to 20 times higher than 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 ricin oil, lactose monohydrate, microcrystalline cellulose, tartaric acid, povidone, anhydrous colloidal silica, magnesium stearate.

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

6.2 Incompatibilities

Not relevant.



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6.3 Shelf-life

Heat-formed blister pack (PVC/aluminium): 2 years

Bottle (polypropylene): 3 years

6.4 Special precautions for storage

Store below $\pm 25^{\circ}\text{C}$.

Store in a dry place in original packaging.

6.5 Nature and contents of container

4, 7, 10, 15, 20, 30, 50 or 100 tablets in heat-formed blister packs (PVC/aluminium).

4, 7, 10, 15, 20, 30, 50 or 100 tablets in bottles (polypropylene) with stoppers (PE).

6.6 Instructions for use and handling

Do not use any tablets if their color has changed.

7. Marketing Authorization Holder

SANOFI-SYNTHELABO FRANCE

174, avenue de France

75013 FRANCE

8. Presentations And Administrative Identification Numbers

345 620-3: 4 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 345 622-6: 7 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 343 074-1: 10 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 343 075-8: 15 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 345 623-2: 20 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 343 076-4: 30 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 345 624-9: 50 film-coated tablets in heat-formed blister pack (PVC/aluminium)
 560 866-3: 100 film-coated tablets in heat-formed blister pack (PVC/aluminium)

345 625-5: 4 film-coated tablets in bottle (polypropylene) with stopper (PE)
 345 626-1: 7 film-coated tablets in bottle (polypropylene) with stopper (PE)
 343 077-0: 10 film-coated tablets in bottle (polypropylene) with stopper (PE)
 343 078-7: 15 film-coated tablets in bottle (polypropylene) with stopper (PE)
 345 627-8: 20 film-coated tablets in bottle (polypropylene) with stopper (PE)
 343 079-3: 30 film-coated tablets in bottle (polypropylene) with stopper (PE)
 345 628-4: 50 film-coated tablets in bottle (polypropylene) with stopper (PE)
 560 868-6: 100 film-coated tablets in bottle (polypropylene) with stopper (PE)

9. Date Of First Authorization/Renewal Of The Authorization

10. Date Of Approval/Revision

April 2003

PRESCRIPTION AND DISPENSING CONDITIONS

List I

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר.

The format of this leaflet has been determined by the Ministry of health and its content has been examined and approved.

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