CPMP/1034/96-EN
EMEA/H/A/002/00/0/0

OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS PURSUANT TO ARTICLE 10 OF COUNCIL DIRECTIVE 75/319/EEC AS AMENDED

Medicinal product

Names:	MIZOLLEN
International non-proprietary name:	Mizolastine
Pharmaceutical form:	Modified release tablet
Strength:	10mg
Route of administration:	Oral
Packaging and package sizes:	Aluminium PVC blisters : 10, 15 or 30 tablets Polypropylene tubes/ Polyethylene Caps : 10, 15 or 30 tablets

Basis for opinion

Lorex Synthelabo submitted applications for Mutual Recognition of the Marketing Authorisation granted by the United Kingdom for the above mentioned medicinal product in the framework of Article 9 of Council Directive 75/319/EEC as amended.

The Reference Member State is the United Kingdom.
Member States which have received an application for Mutual Recognition (Concerned Member States) are Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, and Sweden.

The Concerned Member States have not been able to reach an agreement in respect of the Mutual Recognition of the Marketing Authorisation granted by the Reference Member State.

An objection to the authorisation of the medicinal product, Mizollen, on the grounds that the product may present a risk to public health in accordance with Directive 75/319/EEC Article 10.1 was submitted by Sweden to the EMEA on 13/5/96. The objections presented were as follows :

"The Swedish MPA considers that concomitant administration of mizolastine with drugs known to prolong QT-interval such as class I and III antiarrhythmics, neuroleptics and tricyclic antidepressants may be a risk for significant public health hazard. Therefore this should be expressed under 4.3 in the SPC, "Contraindications". Unless this change is introduced into the SPC, the MPA cannot accept the general marketing application of Mizollen.

Additionally , the MPA would prefer "structural and/or functional cardiac disease" instead of "significantly impaired cardiac function" under 4.3 as well as deletion of the sentence
"In clinical trials in which ECG recording was undertaken, no clinically relevant increase in QT interval was observed" under 4.8 in the SPC."

The referral letter is appended to this Opinion.

The Reference Member State sent its report (appended to this opinion) to the EMEA on 15/5/96.

The matter was referred to the CPMP on 22/5/96.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8551
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

On the basis of the objections raised by Sweden (13/5/96) the points to be considered by the CPMP are:

1. There are concerns over the clinical significance of the potential for mizolastine to prolong the QT interval and the potential implications of this for the risk benefit profile of the product and for the SmPC.

Written explanations on the above question were provided by the Marketing Authorisation Holder on the 15/10/96.

An oral explanation was given by the Marketing Authorisation Holder on the 17/12/96.

Opinion
The CPMP, having considered the points of disagreement and the responses provided by the Marketing Authorisation Holder as set out in the appended Arbitration Assessment Report, is of the opinion that:

The Summary of Product Characteristics (SPC) of the Reference Member State, with particular reference to Section 4.3. "Contra-indications" and Section 4.4. "Special warnings and special precautions for use", should be amended as set out in Annex I . The amended SPC as set out in Annex II is considered to adequately address concerns raised regarding the risk/benefit profile of mizolastine and should allow marketing authorisations to be granted in all Concerned Member States.

This opinion is forwarded to the European Commission, to Member States and to the Marketing Authorisation Holder, together with its annexes and appendices.

London, 18 December 1996

On behalf of the CPMP
Prof. J.-M. Alexandre, Chairman

ANNEX I

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Amendments to the Summary of Product Characteristics of the Reference Member State

- Section 4.3 Contraindications

To include:

"or with electrolyte imbalance in particular hypokalaemia" (in place of "or hypokalaemia")
"Clinically significant cardiac disease or a history of symptomatic arrhythmias" (in place of "significant cardiac disease")
"Drugs known to prolong the QT interval such as Class I and Class III anti-arrhythmics"
"Clinically significant bradycardia"
"Concomitant administration of mizolastine with macrolide antibiotics or systemic imidazole antifungals"

- Section 4.4 Special warnings and special precautions for use

To include a revised 1st paragraph as follows:

"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 arryhthmias."

Delete 2nd paragraph

- Section 4.5 Interaction with other medicaments

2nd paragraph to be moved to section 5.2 Pharmacokinetic properties

- Section 4.8 Undesirable effects

1st paragraph to be deleted.

3rd and 5th paragraphs to be merged and repositioned as 4th paragraph.

4th paragraph to have "***certain***" inserted before "***anti-histamines***" and repositioned as 2nd paragraph.

ANNEX II

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

1. NAME OF THE MEDICINAL PRODUCT

Mizollen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Mizolastine (INN) 10mg per tablet
Excipients: qsp. 1 tablet

3. PHARMACEUTICAL FORM

Oblong, white film-coated modified release tablets with a break-bar.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mizolastine is a long-acting H_1 -antihistamine indicated for the symptomatic relief 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 Contra-indications

Hypersensitivity to mizolastine.
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 special 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 any cardiac arrhythmias.
The elderly may be particularly susceptible to the sedative effects of mizolastine and the potential effects of the drug on cardiac repolarisation.

4.5 Interaction with other medicinal products 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, cyclosporin, 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 Use during 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.
In the absence of information on the levels of mizolastine which may appear in human breast milk after administration, mizolastine is not recommended during lactation.

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

The following adverse reactions were reported in decreasing order of frequency in mizolastine-treated patients: drowsiness and asthenia, often transient in nature, and increased appetite associated with weight gain in some individuals. Dry mouth, diarrhoea, dyspepsia or headache may occur. Isolated cases of hypotension, anxiety and depression, low neutrophil count and raised liver enzymes have been reported rarely. 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.

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

Mizolastine possesses antihistamine and antiallergic properties due to a specific and selective antagonism of peripheral histamine H_1 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 P_{450} 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 :
Hydrogenated castor oil, lactose, microcrystalline cellulose, tartaric acid, polyvidone, anhydrous colloidal silica, magnesium stearate.

Film-coating :
Methylhydroxypropyl cellulose, titanium dioxide, propylene glycol.

6.2 Incompatibilities

None stated

6.3 Shelf-life

2 years in blisters.
3 years in securitainers.

6.4 Special precautions for storage

Store in a dry place below 25 C.
Tablets should not be taken if they become discoloured.

6.5 Nature and content of container

Aluminium/PVC blisters	Packs of 10, 15 or 30 tablets
Polypropylene tubes with polyethylene caps	Packs of 10, 15 or 30 tablets

6.6 Instructions for use and handling, and disposal (if appropriate)

None stated

7. MARKETING AUTHORISATION HOLDER

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX III

OVERALL SCIENTIFIC SUMMARY

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MIZOLLEN

There were concerns over the clinical significence of the potential for mizolastine to prolong the QT interval and the potential implications of this for the risk benefit profile of the product and for the SmPC.
Before assessing the applicant's response to these concerns a number of important methodological and clinical issues associated with QT interval prolongation were reviewed including normal values, spontaneous variability in the QT interval and proarrhythmic prolongation of the QT interval associated with both cardiovascular and non-cardiovascular drugs. Reference was made to the draft recommendations of the CPMP ad-hoc working group on the QT interval and in particular the predictive value of preclinically and clinically documented prolongation of the QT interval for the induction of torsades de pointes and malignant ventricular arrhythmias .

Conclusions

- Although the effects of mizolastine on the QT interval are weak and within the values that may be observed spontaneously mizolastine appears to have a weak but perceptible potential to prolong the QT interval.

- In this respect, mizolastine is probably marginally more potent than loratadine and it appears that the potential to prolong the QT interval is very close and ranks as follows:
  Mizolastine ≥ Loratadine ≥ Placebo

- No patient on mizolastine developed a QT interval value in excess of 480 msecs and no objectively documented serious arrhythmias were reported.

- In terms of their potential to prolong the QT interval and induce torsades de pointes, mizolastine is far less potent that terfenadine and astemizole.

- The clinical data are in sharp contrast to the *in vitro* preclinical data and emphasise the limitations of the *in vitro* preclinical investigations when carried out under inappropriate conditions such as low stimulation rates. The *in vivo* extrapolation of *in vitro* data is further hampered by significant physico-chemical differences between the drugs which are compared in *in vitro* investigations.

- The original concern of the Reference Member State arose from the observation of 5 patients in long-term study who showed mild/moderate prolongation of the QT interval. Further data now provided on these 5 patients remove much of these concerns. However, until postmarketing experience with clinical use of mizolastine is accumulated, a cautious approach to its use may be considered advisable.

- Following a CPMP ad-hoc breakout meeting and the oral explanation provided by the company a number of amendments were made to the SPC as detailed in Annex I of the CPMP Opinion. The proposed SPC (Annex II to the CPMP Opinion) is now considered to provide sufficient safeguards for the high risk population.

- The CPMP having considered the written response provided by the company, the Rapporteur/Co-Rapporteur's joint assessment report, comments from CPMP members, the report from the ad-hoc break-out group and the oral explanation of the company were of the Opinion that the objections raised by Sweden should not prevent the granting of a marketing authorisation but that the SmPC should be amended as set out in Annex I of the CPMP Opinion.