SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRIMALAN 10 mg, scored tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mequitazine ..... 10 mg
for one scored tablet.

Excipients: lactose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of allergy:
- (seasonal or perennial) allergic rhinitis,
- conjunctivitis,
- urticaria.

4.2. Posology and method of administration

Oral use.
FOR ADULTS ONLY

- Adults: 10 mg per day in 1 or 2 doses

o either 1 tablet in the evening
o or 1/2 a tablet morning and evening.
The 10-mg tablets are not suitable for children.

It may be preferable to take the medicine in the evening because of the possible sedative effects of mequitazine in some sensitive subjects (children, elderly subjects).

4.3. Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- concomitant treatment with a medicinal product known to prolong the QT interval (see section 4.5),
- patients with congenital long QT syndrome,
- patients with known or suspected QT interval prolongation or electrolyte imbalance, particularly hypokalaemia,
- clinically significant bradycardia,
- history of agranulocytosis related to intake of phenothiazines,
- risk of closed-angle glaucoma,
- risk of urinary retention related to urethro-prostatic disorders.
- lactating women.

4.4. Special warnings and precautions for use

Special warnings

- Primalan is a racemate the L-enantiomer of which (levomequitazine), in a specific clinical study with ECG, demonstrated significant QT interval prolongation, particularly among poor cytochrome P450 2D6 (CYP2D6) metabolisers;

Under these conditions, Primalan should be used with caution after ten days, owing to the risk of accumulation of the L-enantiomer (levomequitazine).
Use of Primalan should not be recommended among patients known to be poor cytochrome P450 2D6 (CYP2D6) metabolisers, or taking medicinal products which inhibit CYP2D6 (paroxetine, fluoxetine, bupropion, duloxetine, terbinafine, cinacalcet) (see section 4.5). By analogy with the kinetics of levomequitazine, high blood concentrations in these patients may give rise to a risk of QT prolongation.

- In view of this risk, intake of mequitazine with methadone, certain neuroleptics and certain antiparasitic agents is not recommended (see section 4.5).
- Intake of this medicinal product is not recommended with alcoholic beverages or medicinal products containing alcohol (see section 4.5).
- The use of this medicinal product with sodium oxybate is not recommended, due to the risk of increased central nervous system depression (see section 4.5.)
- If symptoms persist or worsen, therapeutic management should be reassessed.
- Cases of agranulocytosis have been described with phenothiazines. The patient should be warned that in the event of fever or an infection under treatment, he or she should consult a doctor as soon as possible. In the event of marked changes to the blood count, treatment should be discontinued.
- This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions for use

Mequitazine should be used with caution and intensified surveillance in the following patients:

- elderly subjects, because of their higher sensitivity to sedation,
- severe hepatic insufficiency, because of the risk of reduced clearance and an accumulation of mequitazine,
- epileptic subjects, because of possible lowering of the seizure threshold, known to occur with phenothiazines.

4.5. Interaction with other medicinal products and other forms of interaction

Drugs liable to induce torsades de pointes:

This serious type of cardiac arrhythmia may be caused by a number of medicinal products, which may or may not have an antiarrhythmic effect.

Hypokalaemia (see potassium-depleting agents) is a predisposing factor, as is bradycardia (see bradycardia-inducing agents) or congenital or acquired pre-existing QT interval prolongation.

The medicinal products concerned notably include class Ia and III antiarrhythmic agents and certain neuroleptics. For dolasetron, erythromycin, spiramycin and vincamine, only the intravenous forms lead to this interaction.

The concomitant use of ~~a~~ more than one torsadogenic medicinal product is contraindicated as a general rule.

However, methadone and certain other sub-categories are an exception to the rule:

- antiparasitic agents (chloroquine, halofantrine, lumefantrine, pentamidine) are only advised against with other medicinal products which induce torsades de pointes;
- neuroleptics liable to induce torsades de pointes are also advised against, but not contraindicated, with other medicinal products which induce torsades de pointes.
  However, citalopram, escitalopram, domperidone and hydroxyzine remain contraindicated with all torsadogenics.

Contraindicated combinations (see section 4.3)

+ Other medicinal products which induce torsades de pointes (other than antiparasitic agents and neuroleptics liable to induce torsades de pointes, and methadone, see "inadvisable combinations"): (such as: amiodarone, products containing arsenic, artenimol

(dihydroartemisinin), bepridil citalopram, cisapride, diphemanil, disopyramide, dofetilide, IV dolasetron, domperidone, dronedarone, IV erythromycin, escitalopram, hydroquinidine, hydroxyzine, ibutilide, ~~levofloxacine,~~ mizolastine, moxifloxacin, piperaquine, prucalopride, quinidine, sotalol, IV spiramycin, toremifene, vandetanib, IV vincamine)
Increased risk of ventricular arrhythmias, especially torsades de pointes.

Inadvisable combinations (see section 4.4)

+ Antiparasitic agents liable to induce torsades de pointes (chloroquine, halofantrine, lumefantrine, pentamidine)
Increased risk of ventricular arrhythmias, especially torsades de pointes. Discontinue one of the two treatments if possible. If combination cannot be avoided, prior control of QT and ECG surveillance.

+ **Methadone**
Increased risk of ventricular arrhythmias, especially torsades de pointes.

+ **Neuroleptics liable to induce torsades de pointes (amisulpride, chlorpromazine, cyamemazine, droperidol, fluphenazine, flupentixol, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sertindole, sulpiride, sultopride, tiapride, zuclopenthixol)**
Increased risk of ventricular arrhythmias, especially torsades de pointes.

+ **Paroxetine, fluoxetine**
Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by paroxetine or fluoxetine.

+ **Bupropion**
Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by bupropion.

+ **Duloxetine**
Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by duloxetine.

+ **Cinacalcet**
Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by cinacalcet.

+ **Terbinafine**
Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by terbinafine.

+ Alcohol
Increase in the sedative effect of mequitazine due to alcohol. Driving and operating machines may be hazardous owing to impaired alertness.

+ Sodium oxybate
Increased central nervous system depression. Impaired concentration can make it dangerous to drive vehicles and use machines.

Combinations requiring precautions for use

+ **Anagrelide**
Increased risk of ventricular arrhythmias, especially torsades de pointes. ECG and clinical surveillance during combination.

+ **Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)**
Increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and ECG monitoring.

+ **Bradycardia-inducing agents**
Increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and ECG monitoring.

+ **Azithromycin, clarithromycin, roxithromycin**
Increased risk of ventricular arrhythmias, especially torsades de pointes. ECG and clinical surveillance during combination.

+ Ciprofloxacin, levofloxacin, norfloxacin
Increased risk of ventricular rhythm disorders, especially torsades de pointes. Clinical and ECG monitoring during combination therapy.

+ **Potassium-depleting agents [potassium-depleting diuretics, alone or in combination, stimulant laxatives, glucocorticoids, tetracosactide and amphotericin B (IV use)].**
Increased risk of ventricular arrhythmias, especially torsades de pointes. Any existing hypokalaemia should be corrected before administration, and clinical, electrolyte and ECG surveillance implemented.

+ Ondansetron
Increased risk of ventricular rhythm disorders, especially torsades de pointes. Clinical and ECG monitoring during combination therapy.

Combinations to be taken into account

+ Muscarinic antagonists
Tricyclic antidepressants, most H1-antihistamines, anticholinergic antiparkinson agents, antispasmodics, disopyramide, phenothiazine neuroleptics and clozapine:

Additive effect on adverse effects such as urinary retention, acute glaucoma, constipation and dry mouth.

+ Sedatives
Morphine derivatives (analgesics, antitussives and replacement therapies), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepine anxiolytics (e.g. meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1-antihistamines, centrally acting antihypertensives, baclofen and thalidomide:

Increased central nervous system depression. Impaired concentration can make it dangerous to drive vehicles and use machines.

4.6. Pregnancy and breastfeeding

Pregnancy

There are insufficient animal studies to draw any conclusions regarding reproductive toxicity (see section 5.3).

There are currently no sufficiently relevant clinical data to assess the risk of malformation or foetal toxicity due to mequitazine administered during pregnancy.

In newborns of mothers treated with long-term, high-dose anticholinergic medicinal products, there have been rare reports of signs linked to muscarinic properties (abdominal distension, meconium ileus, delayed passage of meconium, initial feeding problems, tachycardia, neurological disorders etc.).

Based on these data, Primalan is not recommended for use during pregnancy and in women of childbearing potential who are not using contraception.

If this medicinal product is administered in late pregnancy, it would be sensible to monitor the newborn's neurological and digestive functions for a period.

Breastfeeding

It is not known whether mequitazine or its metabolites pass into breast milk.

Given the potential for sedation or paradoxical excitement in the newborn, and the risks of sleep apnoea associated with phenothiazines, a risk to breastfed newborns/infants cannot be ruled out.

Mequitazine is contraindicated in breastfeeding women.

4.7. Effects on ability to drive and use machines

The attention of patients, particularly those who drive or operate machinery, should be drawn to the risk of drowsiness associated with this medicine, especially at the beginning of treatment.

This phenomenon is emphasised by intake of alcoholic beverages or medicines containing alcohol.

Treatment should preferably be started in the evening.

4.8. Undesirable effects

The following undesirable effects, by system organ class, have been reported (frequency not known).

System organ class (MedDRA classification)	Undesirable effects
Immune system disorders	• Anaphylactic shock
Psychiatric disorders	• Hallucinations, particularly among elderly subjects • Nervousness
Nervous system disorders	• Sedation or drowsiness, more marked at the start of treatment • Mental confusion, particularly among elderly subjects • Agitation • Hyperstimulation • Insomnia • Acute dyskinesia • Cases of extrapyramidal syndrome have been reported with phenothiazines
Eye disorders	• Accommodation disorders • Mydriasis
Cardiac disorders	• Tachycardia • A publication reported a case of torsades de pointes in a patient with congenital long QT syndrome during combined therapy with mequitazine and a macrolide
Gastrointestinal disorders	• Dry mouth • Constipation
Skin and subcutaneous tissue disorders	• Photosensitivity reactions • Erythema • Eczema • Pruritus • Purpura • Urticaria • Angioneurotic oedema
Renal and urinary disorders	• Risk of urinary retention

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

In the event of overdose, general surveillance of symptoms, with cardiac monitoring, including QT interval and heart rate for 48 hours, is recommended.

Risk of seizures, particularly in children.

Consciousness disturbances, coma.

Symptomatic treatment in a specialised environment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ANTIHISTAMINE FOR SYSTEMIC USE

(D: Dermatology)

(R: Respiratory system)

Mequitazine is a phenothiazine H_1 antihistamine characterised by:

- a sedative effect of histaminergic and central adrenolytic origin, which is less potent than that of other first-generation H_1 antihistamines.
The absence of sedation was evidenced at a dose of 5 mg on a limited number of healthy volunteers. This cannot be verified in certain more sensitive subjects (children, the elderly).
Mequitazine is usually non-sedative at a dosage of 5 mg, but has a narrow therapeutic margin since it exerts a sedative effect at 10 mg.
- an anticholinergic effect, responsible for peripheral adverse effects.

Antihistamines have in common the property of counteracting the effects of histamine by competitive antagonism.

5.2. Pharmacokinetic properties

Mequitazine is rapidly absorbed.

The apparent elimination half-life, after repeated doses, is 18 hours.

The apparent volume of distribution is high, indicating very high diffusion of mequitazine into the extravascular environment. Biotransformation is the primary route of elimination of the product. Mequitazine and its metabolites are mainly excreted by the biliary route. Urinary excretion of mequitazine in the unchanged form is very low.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and genotoxicity studies.
Effects in repeated dose toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Reproductive toxicity studies conducted with Mequitazine did not evidence any effect on fertility in males and females. Concerning embryo-toxicity and post natal development, animal data are insufficient to assess the risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, maize starch, arabic gum, colloidal anhydrous silica, talc, sodium carboxymethylstarch , magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store below 25°C and protected from light.

6.5. Nature and contents of container

[Item to be completed by the Marketing Authorisation Holder]

6.6. Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
45, PLACE ABEL GANCE
92100 BOULOGNE
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

30/07/2015

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.