1. NAME OF THE MEDICINAL PRODUCT
PRIMALAN, syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Mequitazine ..... 0.05 g in 100 ml of syrup.
One 2.5-ml measuring spoon contains 1.25 mg of mequitazine.
Excipients: methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sucrose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Syrup.

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 USE IN ADULTS AND CHILDREN OVER THE AGE OF 2 YEARS ONLY
The use in children under 2 years old is contraindicated (see section 4.3)
The available information on population between 2-6 years is limited in clinical trials.
One 2.5-ml measuring spoon contains 1.25 mg of mequitazine.
The daily dose, depending on body weight, is:
• below a weight of 40 kg: one 1.25 mg measuring spoon per 5 kg weight.
• above 40 kg: 8 x 1.25 mg measuring spoons.
The daily dose is to be divided into one or two intakes a day.
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 (such as: amiodarone, products containing arsenic, diphenamid, disopyramide, IV dolasetron, doxilide, dronedarone, IV erythromycin, hydroquinidine, ibutilide, mizolastine, moxifloxacin, quinidine, sotalol, IV spiramycin, toremifene, IV vincamine) (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 phe-nothiazines,
• risk of closed-angle glaucoma,
• risk of urinary retention related to urethro-prostatic disorders.
• children under 2 years old
• 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).
• 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 "parahydroxybenzoate" and may cause allergic reactions (possibly delayed).
• This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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. As regards erythromycin, spiramycin and vincamine, this interaction only concerns the intravenously administered forms.
Use of a medicinal product which induces torsades de pointes with another drug having the same effect is generally contraindicated.
However, methadone and certain other sub-categories are an exception to the rule:
• antiparasitic agents (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.

Sedative drugs
The fact that numerous medicinal products or substances may have additive CNS depressant effects and reduce alertness should be taken into account. These include morphine derivatives (analgesics, cough suppressants and substitute treatments), neuroleptics, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (e.g. meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1 antihistamines, centrally acting antihypertensive agents, baclofen and thalidomide.

Atropine-like substances
The fact that atropine-like substances may have additive undesirable effects, and more readily induce urinary retention, acute episodes of glaucoma, constipation, dry mouth, etc., should be taken into account.
Different atropine-like substances include imipramine antidepressants, the majority of atropine-like H1 antihistamines, anticholinergic antiparkinsonian agents, atropine-like antispasmodics, disopyramide, phenothiazine neuroleptics, together with clozapine.

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...
pointes, and methadone, see “inadvisable combinations”): (such as: amiodarone, products containing arsenic, citalopram, diphenamid, disopyramide, dofeutilide, IV dolasetron, domperidone, dronedarone, IV erythromycin, escitalopram, hydroquinidine, ibutilide, levofloxacine, mizolastine, moxifloxacine, prucalopride, quinidine, sotalol, IV spiramycin, toremifene, IV vincamine) Increased risk of ventricular arrhythmias, especially torsades de pointes.

<table>
<thead>
<tr>
<th>Inadvisable combinations (see section 4.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Antiparasitic agents liable to induce torsades de pointes (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.</td>
</tr>
<tr>
<td>+ Methadone Increased risk of ventricular arrhythmias, especially torsades de pointes.</td>
</tr>
<tr>
<td>+ Neuroleptics liable to induce torsades de pointes (amisulpride, chlorpromazine, cyamemazine, droperidol, fluphenazine, flupentixol, haloperidol, levomepromazine, pimozide, pipamperone, pipotiazine, sulpiride, sultopride, tiapride, zuclophenthixol) Increased risk of ventricular arrhythmias, especially torsades de pointes.</td>
</tr>
<tr>
<td>+ Paroxetine, fluoxetine Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by paroxetine or fluoxetine.</td>
</tr>
<tr>
<td>+ Bupropion Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by bupropion.</td>
</tr>
<tr>
<td>+ Duloxetine Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by duloxetine.</td>
</tr>
<tr>
<td>+ Cinacalcet Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by cinacalcet.</td>
</tr>
<tr>
<td>+ Terbinafine Risk of exacerbation of the undesirable effects of mequitazine, due to inhibition of its metabolism by terbinafine.</td>
</tr>
<tr>
<td>+ Alcohol Increase in the sedative effect of mequitazine due to alcohol. Driving and operating machines may be hazardous owing to impaired alertness. Avoid consumption of alcoholic beverages and medicinal products containing alcohol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combinations requiring precautions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Azithromycin Increased risk of ventricular arrhythmias, especially torsades de pointes. ECG and clinical surveillance during combination.</td>
</tr>
<tr>
<td>+ Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol, nebivolol) Increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and ECG monitoring.</td>
</tr>
<tr>
<td>+ Bradycardia-inducing agents Increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and ECG monitoring.</td>
</tr>
<tr>
<td>+ Clarithromycin Increased risk of ventricular arrhythmias, especially torsades de pointes. ECG and clinical surveillance during combination.</td>
</tr>
<tr>
<td>+ 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.</td>
</tr>
<tr>
<td>+ Roxithromycin Increased risk of ventricular arrhythmias, especially torsades de pointes. ECG and clinical surveillance during combination.</td>
</tr>
</tbody>
</table>

**4.6. Pregnancy and lactation**

**Pregnancy**

There are no or limited amount of data from the use of Mequitazine in pregnant women. Animal studies
are insufficient with respect to reproductive toxicity (see section 5.3). Primalan is not recommended during pregnancy and in women of childbearing potential not using contraception.

**Lactation**
It is unknown whether Mequitazine / metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Primalan is contraindicated during breast-feeding (see section 4.3)

**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).

<table>
<thead>
<tr>
<th>System organ class (MedDRA classification)</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic shock</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Hallucinations, particularly among elderly subjects</td>
</tr>
<tr>
<td></td>
<td>Nervousness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Sedation or drowsiness, more marked at the start of treatment</td>
</tr>
<tr>
<td></td>
<td>Mental confusion, particularly among elderly subjects</td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
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<tr>
<td></td>
<td>Hyperstimulation</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Acute dyskinesia</td>
</tr>
<tr>
<td></td>
<td>Cases of extrapyramidal syndrome have been reported with phenothiazines</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Accommodation disorders</td>
</tr>
<tr>
<td></td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
</tbody>
</table>

**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 authorisation 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 Ansm (French National Agency for security of medicines and health products) and Regional Centers of Pharmacovigilance.
Website: www.ansm.sante.fr

**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 infants and 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 H1 antihistamine characterised by:
- a sedative effect of histaminergic and central adrenergic origin, which is less potent than that of other first-generation H1 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 extracellular 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
Ascorbic acid, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), soluble mandarin essence, sucrose, purified water.

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months, protected from light.

6.4. Special precautions for storage
Do not use PRIMALAN, syrup, after the expiry date which is stated on the bottle. Store protected from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.5. Nature and contents of container
60 ml in a bottle (tinted glass) with a 2.5-ml measuring spoon.
120 ml in a bottle (tinted glass) with a 2.5-ml measuring spoon.
125 ml in a bottle (tinted glass) with a 2.5-ml measuring spoon.

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

8. MARKETING AUTHORISATION NUMBER(S)
• 3400932636808: 60 ml in a bottle (tinted glass) + measuring spoon
• 3400934734663: 120 ml in a bottle (tinted glass) + measuring spoon
• 3400936273085: 125 ml in a bottle (tinted glass) + measuring spoon

10. DATE OF REVISION OF THE TEXT
12/6/2014