Core Safety Profile

Active substance: Chlorpromazine
Pharmaceutical form(s)/strength: 10mg, 25mg, 50mg and 100mg fim-coated or uncoated tablets
5mg/ml syrup, 10mg/ml and 20mg/ml suspension forte, 40mg/ml oral drops
5mg/ml and 25mg/ml injectable solution
25mg and 100mg suppositories

P-RMS: FR/H/PSUR/0065/001
Date of FAR: 26.10.2012
4.3 CONTRAINDICATIONS

- Hypersensitivity to chlorpromazine or one of the other constituents.
- Risk of angle-closure glaucoma.
- Risk of urinary retention related to urethroprostatic disorders.
- History of agranulocytosis
- Dopaminergic antiparkinsonism agents (see Section 4.5).
- Nursing mothers (see Section 4.6).
- Gluten allergy or intolerance (see Section 4.4)
- Citalopram, escitalopram

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

All patients must be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment will be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the latter.

Neuroleptic malignant syndrome: treatment must be interrupted in the event of unexplained hyperpyrexia since this can be one of the signs of neuroleptic malignant syndrome (pallor, hyperthermia, disorders of autonomic function). Signs of autonomic instability, such as hyperhydrosis and irregular blood pressure, can precede the onset of hyperthermia and as such constitute premonitory signs of this syndrome. While this neuroleptic-related effect can be of idiosyncratic origin, certain risk factors such as dehydration and brain damage would seem to indicate a predisposition.

Neuroleptic phenothiazines may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e. drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment (see Section 4.8).

Where clinically possible, the absence of any factors favoring the onset of ventricular arrhythmias should be ensured before administration:

- bradycardia less than 55 beats per minute;
- hypokalemia;
- congenital long QT interval;
- ongoing treatment with any drug which could induce marked bradycardia (<55 beats per minute), hypokalemia, intracardiac conduction depression or QT prolongation (see section 4.5)

With the exception of emergencies, it is recommended that the initial work up of patients receiving a neuroleptic should include an ECG.
Except under exceptional circumstances, this drug must not be administered to patients with Parkinson's disease.

The concomitant use of chlorpromazine with lithium, other QT prolonging agents, and dopaminergic antiparkinsonism agents is not-recommended (see section 4.5).

The onset of paralytic ileus, potentially indicated by abdominal bloating and pain, must be treated as an emergency (see Section 4.8).

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, <Tradename> should be used with caution in patients with risk factors for thromboembolism (see Section 4.8).

Stroke: In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. <Tradename> should be used with caution in patients with stroke risk factors.

Elderly Patients with Dementia: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Hyperglycaemia or intolerance to glucose has been reported in patients treated with <Tradename>. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on <Tradename> should get appropriate glycaemic monitoring during treatment (see Section 4.8).

- The following populations must be closely monitored after administration of chlorpromazine:
  - epileptics, since chlorpromazine may lower the seizure threshold. Treatment must be discontinued if seizures occur.
  - elderly patients presenting with heightened susceptibility to orthostatic hypotension, sedation and extrapyramidal effects; chronic constipation (risk of paralytic ileus), and potentially prostatic hypertrophy.
  - patients presenting with certain forms of cardiovascular disease, since this class of drug has quinidine-like effects and can induce tachycardia and hypotension.
Patients with severe liver and/or renal failure because of the risk of accumulation.

- Patients on long-term treatment should receive regular ophthalmological and hematological examinations.
- Patients are strongly advised not to consume alcohol and alcohol-containing drugs throughout treatment (see Section 4.5)
- Solution for injection: owing to the risk of hypotension, patients should be advised to remain supine for at least half an hour after injection.
- Solution for injection: risk of allergic reactions including anaphylactic reactions and bronchospasm owing to the presence of sodium sulfite and disulfite in the formulation.
- Oral solution: since it contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose or galactose malabsorption syndrome, and sucrase-isomaltase deficiency should not take this medicine.
- Oral solution: the alcohol content of the solution must be taken into account. This presentation is not recommended for patients with liver disease or for alcoholics, epileptics and pregnant women.
- The 25 mg and 100 mg tablets contain sucrose and lactose and therefore patients with rare hereditary problems of fructose intolerance, congenital galactosemia, glucose or galactose malabsorption syndrome, sucrase-isomaltase or lactase deficiency, galactose intolerance, the Lapp lactase deficiency should not take this medicine.
- The 25 mg and 100 mg tablets contain wheat starch (gluten) and therefore should not be used in gluten allergy or intolerance.

The following statement may be added in local SPCs according to national requirement only when a paediatric indication exists:

- Since there is a potential impact on cognitive function, children should undergo a yearly clinical examination to evaluate learning capacity. The dosage should be adjusted regularly as a function of the clinical status of the child.
- Because of the risk of choking, the tablets are contraindicated in children under 6.
- The use of the oral solution in children under 6 is reserved for exceptional circumstances in a specialized unit.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Combinations contraindicated
Dopaminergics (quinagolide, cabergoline), not including dopaminergic antiparkinsonism agents, are contraindicated (see Section 4.3) : reciprocal antagonism of the dopaminergic agent and neuroleptic.

Combinations not recommended
Dopaminergic antiparkinsonism agents (amantadine, bromocriptine, cabergoline, levodopa, lisuride, pergolide, piribedil, ropinirole) are not recommended: reciprocal antagonism of the antiparkinsonism agent and neuroleptic (see Section 4.4). Neuroleptic-induced extrapyramidal syndrome should be treated with an anticholinergic rather than a dopaminergic antiparkinsonism agent (dopaminergic receptors blocked by neuroleptics).
Levodopa: reciprocal antagonism of levodopa and the neuroleptic. In Parkinson’s patients, it is recommended to use the minimal doses of each drug.

QT prolonging drugs: there is an increased risk of arrhythmias when chlorpromazine is used with concomitant QT prolonging drugs (including certain antiarrhythmics, and other antipsychotics including sulitopride) and drugs causing electrolyte imbalance (see Section 4.4).

Alcohol: alcohol potentiates the sedative effect of neuroleptics. Changes in alertness can make it dangerous to drive or operate machinery. Alcoholic beverages and medication containing alcohol should be avoided (see Section 4.4).

Lithium (high doses of neuroleptics): concomitant use can cause confusional syndrome, hypertonia and hyperreflexivity, occasionally with a rapid increase in serum concentrations of lithium (see Section 4.4).

Combination requiring precautions
Antidiabetic agents: concomitant administration of high chlorpromazine doses (100 mg/day), and antidiabetic agents can lead to an increase in blood sugar levels (decreased insulin release). Forewarn the patient and advise increased self-monitoring of blood and urine levels. If necessary, adjust the antidiabetic dosage during and after discontinuing neuroleptic treatment.

Topical gastrointestinal agents (magnesium, aluminium and calcium salts, oxides and hydroxides): decreased GI absorption of phenothiazine neuroleptics. Do not administer phenothiazine neuroleptics simultaneously with topical GI agents (administer more than 2 hours apart if possible).

Combination to be taken into consideration
Antihypertensive agents: potentiation of the antihypertensive effect and risk of orthostatic hypotension (additive effects).

Atropine and other atropine derivatives: imipramine antidepressants, histamine H1-receptor antagonists, anticholinergic antiparkinsonism agents, atropinic antispasmodics, disopyramide: build up of atropine-associated adverse effects such as urinary retention, constipation and dry mouth.

Other CNS depressants: morphine derivatives (analgesics, antituissives and substitution treatments), barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, hypnotics, sedative antidepressants, histamine H1 receptor antagonists, central antihypertensive agents increased central depression. Changes in alertness can make it dangerous to drive or operate machinery.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
A large amount of exposure to chlorpromazine during pregnancy did not reveal any teratogenic effect.

It is advised to keep an adequate maternal psychic balance during pregnancy in order to avoid decompensation. If a treatment is necessary to ensure this balance, the treatment should be started or continued at effective dose all through the pregnancy.
Neonates exposed to antipsychotics (including chlorpromazine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

**Lactation:**
Chlorpromazine being excreted in milk, breast-feeding is not recommended during treatment.

**Fertility**
A decrease in fertility was observed in female animals treated with chlorpromazine. In male animals data are insufficient to assess fertility.
In humans, because of the interaction with dopamine receptors, chlorpromazine may cause hyperprolactinaemia which can be associated with impaired fertility in women (see Section 4.8). In men, data on consequences of hyperprolactinaemia are insufficient with regard to fertility.

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
The attention of patients, particularly drivers and machine operators, should be drawn to the risk of drowsiness with this medication especially at the start of treatment.

**4.8 UNDESIRABLE EFFECTS**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10 )</th>
<th>Not known (cannot be estimated from available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
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<td>Agranulocytosis</td>
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<td>Leukopenia</td>
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<tr>
<td>Immune system disorders</td>
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<td>Systemic lupus erythematosus</td>
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<td></td>
<td></td>
<td>Antinuclear antibody positive¹</td>
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<tr>
<td>Endocrine disorders</td>
<td>Hyperprolactinaemia</td>
<td>Amenorrhoea</td>
<td>Galactorrhoea</td>
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<td></td>
<td></td>
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<td>Gynaecomastia</td>
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<td></td>
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<td>Erectile dysfunction</td>
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<td></td>
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<td>Female sexual arousal disorder</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increased</td>
<td>Glucose tolerance impaired (see Section 4.4)</td>
<td>Hyperglycaemia (see Section 4.4)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertriglyceridaemia</td>
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<td></td>
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<td>Hyponatraemia</td>
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<td></td>
<td></td>
<td></td>
<td>Inappropriate antiuretic hormone secretion</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td></td>
<td>Lethargy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mood altered</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Sedation²</td>
<td>Hypertonia</td>
<td>Torticollis</td>
</tr>
<tr>
<td></td>
<td>Somnolence²</td>
<td>Convulsion</td>
<td>Oculogyric crisis</td>
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<tr>
<td></td>
<td>Dyskinesia</td>
<td></td>
<td>Trismus</td>
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<td></td>
<td>Tardive dyskinesia³</td>
<td></td>
<td>Akinesia</td>
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<tr>
<td></td>
<td>Extrapyramidal disorder</td>
<td></td>
<td>Hyperkinesia</td>
</tr>
<tr>
<td></td>
<td>Akathisia</td>
<td></td>
<td>Neuroleptic malignant syndrome (see Section 4.4)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Cardiac disorders</td>
<td>Vascular disorders</td>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Accommodation disorder Deposit eye</td>
<td>Electrocardiogram QT prolonged (see Section 4.4)</td>
<td>Orthostatic hypotension</td>
<td>Dry mouth Constipation (see Section 4.4)</td>
</tr>
<tr>
<td>Ventricular arrhythmia Ventricular fibrillation Ventricular tachycardia Torsade de pointes Cardiac arrest Sudden death / Sudden cardiac death (with possible causes of cardiac origin as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines) (see Section 4.4)</td>
<td></td>
<td>Embolism venous Pulmonary embolism (sometimes fatal) Deep vein thrombosis (see Section 4.4)</td>
<td>Colitis ischaemic Ileus paralytic (see Section 4.4) Intestinal perforation (sometimes fatal) Gastrointestinal necrosis (sometimes fatal) Necrotising colitis (sometimes fatal) Intestinal obstruction</td>
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</tbody>
</table>

7/08
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<tr>
<th>breast disorders</th>
<th>General disorders and administration site conditions</th>
<th>Temperature regulation disorder</th>
</tr>
</thead>
</table>

1 may be seen without evidence of clinical disease  
2 particularly at the start of treatment  
3 particularly during long term treatment; may occur after the neuroleptic is withdrawn and resolve after reintroduction of treatment or if the dose is increased  
4 in the anterior segment of the eye caused by accumulation of the drug but generally without any impact on sight

- Tablets: risk of allergic reactions owing to the presence of orange yellow S in the formulation.  
- Solution for injection: risk of allergic reactions including anaphylactic reactions and bronchospasm owing to the presence of sodium sulfite and disulfite in the formulation.

**4.9 OVERDOSE**

Parkinsonism, convulsions, coma.  
Symptomatic treatment, continuous respiratory and cardiac monitoring (risk of prolonged QT interval) until the patient's condition resolves.