Core Safety Profile
chlorprothixene /Truxal
tablets 5 mg, 15 mg, 25 mg, 50 mg, 100 mg

4.2 Posology and method of administration

Children and adolescents
Chlorprothixene is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance, other thioxanthenes or to any of the excipients (see section 6.1).

Circulatory collapse, depressed level of consciousness due to any cause (e.g. intoxication with alcohol, barbiturates or opiates), coma.

As with other drugs belonging to the therapeutic class of antipsychotics, chlorprothixene can cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, Truxal is contraindicated in patients with a history of clinically significant cardiovascular disorders (e.g. significant bradycardia (<50 beats per minute), recent acute myocardial infarction, uncompensated heart failure, cardiac hypertrophy, arrhythmias treated with class 1A and III antiarrhythmic products) and in patients with a history of ventricular arrhythmias or Torsade de Pointes.

Truxal is contraindicated in patients with known uncorrected hypokalaemia, and those with known uncorrected hypomagnesaemia.

Furthermore, Truxal is contraindicated in patients with congenital long QT syndrome, or in patients with known acquired QT interval prolongation (QTc above 450 msec in males and 470 msec in females).

Truxal is contraindicated in patients receiving drugs known to significantly prolong the QT interval (See section 4.5).

4.4 Special warnings and precautions for use

The possibility of development of neuroleptic malignant syndrome (hyperthermia, muscle rigidity, fluctuating consciousness, instability of the autonomous nervous system) exists with any neuroleptic. Patients with pre-existing organic brain syndrome, mental retardation, opiate and alcohol abuse are over-represented among fatal cases.

Treatment: Discontinuation of the neuroleptic. Symptomatic treatment and use of general supportive measures. Dantrolene and bromocriptine may be helpful. Symptoms may persist for more than a week after oral neuroleptics.
Attacks of acute glaucoma due to dilation of the pupil may occur in patients with the rare condition of shallow anterior chamber and narrow chamber angle.

Due to the risk of malignant arrhythmias, chlorprothixene should be used with caution in patients with a history of cardiovascular disease or family history of QT prolongation.

ECG monitoring is mandatory prior to treatment. Chlorprothixene is contraindicated if a QTc interval of more than 450 msec in males or 470 msec in females is observed at baseline (See section 4.3). During therapy, the need for ECG monitoring should be assessed on an individual patient basis. Whilst on therapy, reduce dose if QT is prolonged and discontinue therapy if QTc is >500 ms.

Periodic electrolyte monitoring is recommended.

Concomitant treatment with other antipsychotics should be avoided (see section 4.5).

Like other neuroleptics chlorprothixene should be used with caution in patients with organic brain syndrome, convulsion and advanced hepatic, renal and cardiovascular disease. Furthermore, in patients with myasthenia gravis and benign prostatic hypertrophy.

Precaution for use are required in patients with:
- Pheochromocytoma
- Prolactin-dependent neoplasia
- Severe hypotension or orthostatic dysregulation
- Parkinson disease
- Diseases of the hemopoietic system
- Hyperthyreosis
- Micturition disorders, urinary retention, pylorus stenosis, ileus.

As described for other psychotropics chlorprothixene may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients.

Patients on long-term therapy, particularly on high doses, should be monitored carefully and evaluated periodically to decide whether the maintenance dosage can be lowered.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with chlorprothixene and preventive measures undertaken.

Use in children and adolescents under 18 years of age

Chlorprothixene is not recommended for use in the treatment of children and adolescents.

No sufficient studies in regard to efficacy and safety of chlorprothixen in children and adolescents are available. Therefore chlorprothixen shall be prescribed for children and
adolescents (< 18) only, if there is a stringent indication and after careful benefit-risk assessment is mentioned.

Elderly Cerebrovascular
An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Chlorprothixene should be used with caution in patients with risk factors for stroke.

Elderly patients are particularly susceptible to orthostatic hypotension.

Increased Mortality in Elderly people with Dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Chlorprothixene is not licensed for the treatment of dementia-related behavioural disturbances.

Excipients
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations requiring precautions for use
Chlorprothixene may enhance the sedative effect of alcohol and the effects of barbiturates and other CNS depressants.
Neuroleptics may increase or reduce the effect of antihypertensive drugs; the antihypertensive effect of guanethidine and similarly acting compounds is reduced.
Concomitant use of neuroleptics and lithium increases the risk of neurotoxicity.
Tricyclic antidepressants and neuroleptics mutually inhibit the metabolism of each other.
Chlorprothixene may reduce the effect of levodopa and the effect of adrenergic drugs and enhance the effect of anticholinergics.
Concomitant use of metoclopramide and piperazine increases the risk of extrapyramidal disorder.
The antihistaminergic effect of chlorprothixene may diminish or eliminate the alcohol/disulfiram reaction.

Increases in the QT interval related to antipsychotic treatment may be exacerbated by the co-administration of other drugs known to significantly increase the QT interval. Co-
administration of such drugs is therefore contraindicated (see section 4.3). Relevant classes include:
- class Ia and III antiarrhythmics (e.g. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g. thioridazine)
- some macrolides (e.g. erythromycin)
- some antihistamines (e.g. terfenadine, astemizole)
- some quinolone antibiotics (e.g. gatifloxacin, moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly increase QT interval (e.g. cisapride, lithium) are also contraindicated.

Drugs known to cause electrolyte disturbances such as thiazide diuretics (hypokalaemia) and drugs known to increase the plasma concentration of chlorprothixene should also be avoided as they may increase the risk of QT prolongation and malignant arrhythmias (See section 4.3).

Neuroleptics are metabolised in the Cytochrome P450 system of the liver. Drugs, which inhibit the Cytochrome CYP 2D6 system (e.g.: paroxetine, fluoxetine, chloramphenicol, disulfiram, isoniazide, MAO-Inhibitors, oral contraceptives, in lower degree buspirone, sertraline or citalopram) can increase the plasma level of chlorprothixene. Concomitant use of Truxal and drugs with known anticholinergic activity enhances anticholinergic effects.

**4.6 Pregnancy and lactation**

*Pregnancy*
Clinical experience of use in pregnant women is limited. Chlorprothixene should not be administered during pregnancy unless the expected benefit to the patient outweighs the possible risk to the foetus. The newborns of mothers treated with neuroleptics in late pregnancy, or labour, may show signs of intoxication such as lethargy, tremor and hyperexcitability and have a low apgar score.

Animal-reproduction studies have not given evidence of an increased incidence of foetal damage or other deleterious effects on the reproduction process.

*Lactation*
As chlorprothixene is found in breast milk in low concentrations it is not likely to affect the infant when therapeutic doses are used. The dose ingested by the infant is about 2% of the weight related maternal daily dose. Breast-feeding can be continued during chlorprothixene therapy if considered of clinical importance but observation of the infant is recommended, particularly in the first 4 weeks after birth.

**4.7 Effects on ability to drive and use machines**

Truxal is a sedative drug.
Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery.

1. Undesirable effects

Undesirable effects are for the majority dose dependent. The frequency and severity are most pronounced in the early phase of treatment and decline during continued treatment.

Extrapyramidal reactions may occur, especially in the early phase of treatment. In most cases these side effects can be satisfactorily controlled by reduction of dosage and/or use of antiparkinsonian drugs. The routine prophylactic use of antiparkinsonian drugs is not recommended. Antiparkinsonian drugs do not alleviate tardive dyskinesia and may aggravate them. Reduction in dosage or, if possible, discontinuation of chlorprothixene therapy is recommended. In persistent akathisia a benzodiazepine or propranolol may be useful.

Frequencies are taken from the literature and spontaneous reporting. Frequencies are defined as:
very common (1/10), common (1/100 to <1/10), uncommon (1/1000 to <1/100), rare (1/10000 to <1/1000), very rare (<1/10000), or not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Common</th>
<th>Tachycardia, palpitations.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rare</td>
<td>Electrocardiogram QT prolonged.</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Rare</td>
<td>Thrombocytopenia, neutropenia, leukopenia, agranulocytosis.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Somnolence, dizziness</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dystonia, headache.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tardive dyskinesia, parkinsonism, convulsion, akathisia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Neuroleptic malignant syndrome.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common</td>
<td>Accommodation disorder, vision abnormal.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Oculogyration.</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Rare</td>
<td>Dyspnoea.</td>
</tr>
<tr>
<td>Disorder Category</td>
<td>Frequency</td>
<td>Symptoms</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Dry mouth, salivary hypersecretion</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Constipation, dyspepsia, nausea.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vomiting, diarrhoea.</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Micturition disorder, urinary retention.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Hyperhidrosis.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Rash, pruritus, photosensitivity reaction, dermatitis.</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>Myalgia.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Muscle rigidity.</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Rare</td>
<td>Hyperprolactinaemia.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Increased appetite, weight increased.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Decreased appetite, weight decreased.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hyperglycaemia, glucose tolerance impaired.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypotension, hot flush.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Venous thromboembolism.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Asthenia, fatigue.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Hypersensitivity, anaphylactic reaction.</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Uncommon</td>
<td>Liver function test abnormal.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Jaundice.</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>Ejaculation failure, erectile dysfunction.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Gynaecomastia, galactorrhoea, amenorrhoea.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Insomnia, nervousness, agitation, libido decreased.</td>
</tr>
</tbody>
</table>

As with other drugs belonging to the therapeutic class of antipsychotics, rare cases of QT prolongation, ventricular arrhythmias - ventricular fibrillation, ventricular tachycardia, Torsade de Pointes and sudden unexplained death have been reported for chlorprothixene (see section 4.4).

Abrupt discontinuation of chlorprothixene may be accompanied by withdrawal symptoms. The most common symptoms are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation. Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days.

4.9 Overdose

Symptoms
Somnolence, coma, convulsions, shock, extrapyramidal disorder, hyperthermia/hypothermia. In severe cases renal impairment.

ECG changes, QT prolongation, Torsade de Pointes, cardiac arrest and ventricular arrhythmias have been reported when administered in overdose together with drugs known to affect the heart.

Treatment
Treatment is symptomatic and supportive. Gastric lavage should be carried out as soon as possible after oral ingestion and activated charcoal may be administered. Measures to support the respiratory and cardiovascular systems should be instituted. Epinephrine (adrenaline) should not be used as further lowering of blood pressure may result. Convulsions may be treated with diazepam and extrapyramidal disorders with biperiden.

2.5 to 4 g may be fatal, in infants about 4 mg/kg. Adults have survived consummation of 10 g and a 3-year old child 1000 mg.