Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Largactil Injection 2.5% - 2 ml ampoule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlorpromazine hydrochloride 50 mg/2ml (25 mg/ml)

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

A clean, clear solution, colour not deeper than pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Largactil is indicated in the following:

(i) In the management of anxiety and tension states, agitation, depression, behavioural disturbances and subnormality.

(ii) In the management of schizophrenia and other psychoses including mania and hypomania, and psychopathy, and in the control of the central effects of such drugs as LSD.

(iii) In the management of terminal illness, senile irritability, intractable hiccup, eclampsia and pre-eclampsia.

(iv) As a pre- and post-anaesthetic, medication, an adjunct to facilitation of anaesthesia, and induction of hypothermia.

4.2 Posology and method of adminstration

Route of administration: Deep intramuscular injection.

Oral administration should be used whenever possible. Parenteral formulations may be used in emergencies. They may only be administered by deep intramuscular injection. Largactil is too irritant to give subcutaneously. Repeated injections should be avoided if possible.

Table1: Dosage of chlorpromazine in schizophrenia, other psychoses, anxiety and agitation etc.

Route	*Adult*	*Children under 1 year*	*Children 1 -5 years*	*Children 6-12 years*	*Elderly or debilitated patients*
Oral	Initially 25 mg t.d.s. or 75 mg at bedtime increasing by daily amounts of 25 mg to an effective maintenance dose. This is usually in the range 75 to 300 mg daily, but some patients may require up to 1 g daily	Do not use unless need is life saving	0.5mg/kg bodyweight every 4-6 hours to maximum recommended dose of 40 mg daily	1/3 to ½ the adult dose to a maximum recommended dose of 75 mg daily	Start with 1/3 to ½ the usual adult dose with a more gradual increase in dosage
i.m.	For acute relief of symptoms 25-50 mg every 6-8 hours	As above	0.5mg/kg bodyweight every 6-8 hours. Dosage is not advised to exceed 40 mg daily	0.5mg/kg bodyweight every 6-8 hours Dosage is not advised to exceed 40 mg daily	Doses in the lower range for adults should be sufficient to control symptoms i.e. 25 mg 8 hourly

Table 2: Hiccups, Induction of hypothermia

Indication of	*Route*	*Adult dose*	*Children under 1 year*	*Children 1 - 5 years*	*Children 6 -12 years*	*Elderly or debilitated patients*
Hiccups	Oral i.m.	25-50 mg t.d.s. or q.d.s.25-50 mg and if this fails 25-50 mg in 500-1000 ml sodium chloride injection infused slowly	No information available			
Induction of hypothermia to prevent shivering	i.m.	25-50 mg every 6-8 hours	Do not use	Initial dose 0.5 mg to 1 mg/kg. Maintenance of 0.5 mg/kg every 4-6 hours	Initial dose 0.5 mg to 1 mg.kg. Maintenance 0.5 mg/kg every 4-6 hours	No data available

Table 3: Nausea and vomiting of terminal illness

Form	*Adults*	*Children under 1 year*	*Children 1-5 years*	*Children 6-12 years*	*Elderly or debilitated patients*
Oral	10-25mg every 4 -6 hours	Do not use unless need is life saving	0.5 mg/kg every 4-6 hours Maximum daily dosage should not exceed 40 mg	0.5 mg/kg every 4-6 hours maximum daily dosage should not exceed 75 mg	Initially 1/3 to ½ the adult dose. The physician should then use his clinical judgement to obtain control
i.m.	10-25 mg every 4-6 hours until vomiting stops then drugs to be taken orally	Do not use unless need is life saving	0.5 mg/kg 4-6 hours. It is advised that maximum daily dosage should not exceed 40 mg	0.5 mg/kg every 4-6 hours. It is advised that maximum daily dosage should not exceed 75 mg.	Initially 1/3 to ½ the adult dose. The physician should then use his clinical judgement to obtain control.

4.3 Contraindications

1. Hypersensitivity to chlorpromazine or one of the excipients.

2. Risk of angle-closure glaucoma.

3. Risk of urinary retention related to urethroprostatic disorders.

4. Largactil is contraindicated in cases of coma due to direct central nervous system depressants such as alcohol, barbiturates and opiates.

5. Use in patients on concurrent therapy with other drugs potentially haemotoxic.

6. Use in nursing mothers.

7. The tablets contain lactose and are therefore contraindicated in patients with congenital galactosemia, glucose or galactose malabsorption syndrome, and lactase deficiency.

4.4 Special warnings and special precautions for use

Phenothiazines should only be used with great caution in patients with blood dyscrasias.

The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8), and requires immediate haematological investigation.

Except under exceptional circumstances, this drug must not be administered to patients with Parkinson’s disease.

Close monitoring is required in patients with epilepsy or a history of seizures as phenothiazines may lower the seizure threshold.

Phenothiazines should only be used with great caution in patients with a history of jaundice or with existent liver dysfunction and/or renal failure.

Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular attention to potential for inducing eye changes, effects of haemopoiesis, liver dysfunction, myocardial conduction effects particularly if other concurrently administered drugs also have potential effects on these systems.

Patients are strongly advised not to consume alcohol and alcohol-containing drugs throughout treatment.

Chlorpromazine should be used with particular care in the presence of extremes of temperature because of its capacity to interfere with the body's thermoregulator.

The risk-benefit of chlorpromazine treatment should be fully assessed before treatment is commenced and patients with risk factors for ventricular arrhythmias such as cardiac disease, metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesemia; starvation; alcohol abuse or those receiving concomitant therapy with other drugs known to prolong the QT interval, should be monitored carefully (ECGs and potassium levels), particularly during the initial phase of treatment.

Phenothiazines should only be used with great caution in patients with coronary insufficiency or cardiac disease since this class of drug has quinidine-like effects and can induce tachycardia and hypotension.

Neuroleptic malignant syndrome: The syndrome may occur with the use of any neuroleptic agent. Symptoms include clouding of consciousness, rigidity and other extrapyramidal effects, and autonomic dysfunction, most importantly hyperpyrexia. Treatment involves the immediate cessation of neuroleptic therapy and symptomatic management as appropriate.

Administration by the intravenous route may induce local vascular spasm or thromsophlebitis.

The product should not be administered subcutaneously.

4.5 Interaction with other medicinal products and other forms of interaction

The drug may antagonise the effects of anti-Parkinsonian drugs.

There is an increased risk of arrhythmias when antipsychotics are used with drugs which prolong the QT interval including certain antiarrhythmics, antidepressants and other antipsychotics (see section 4.8)

The concomitant administration of this product with other medication such as central nervous system depressant (including alcohol and anaesthetics), or antihypertensives or anticholinergics will result in accentuation of their effects, while potentiation of action will also occur with monamine oxidase inhibitors (MAOIs), antidepressants and analgesics.

The hypotensive effect of chlorpromazine may potentiate the effects of antihypertensives, or of other drugs with hypotensive activity.

Simultaneous administration of prochlorperazine and desferrixoamine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48-72 hours. This may occur with 'LARGACTIL' since it shares many of the pharmacological activities of prochlorperazine.

Combination of chlorpromazine and lithium should be used with care.

Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance the dose of oral hypoglycaemics or of insulin may need to be increased in diabetics.

Antacids: decreased GI absorption of phenothiazine neuroleptics. Do not administer phenothiazine neuroleptics simultaneously with antacids (Administer more than 2 hours apart if possible).

4.6 Pregnancy and lactation

The drug crosses the placenta. Animal studies indicate a teratogenic effect. No clear evidence of such an effect has been shown in man. Phenothiazines should only be used during pregnancy if it is considered essential by the physician. If Largactil is employed in labour it should be withheld until labour is established and the cervix dilated 3-4cm. Chlorpromazine is excreted in breast milk and use in nursing mothers is contraindicated.

4.7 Effects on ability to drive and use machines

Phenothiazines may induce drowsiness. Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

Autonomic disturbances:

- Postural hypotension.
- Anticholinergic effects such as dry mouth, accommodation disorders, risk of urinary retention, constipation and even paralytic ileus (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Neuropsychiatric disorders:

- Sedation or drowsiness, particularly at the start of treatment.

Use of phenothiazines at high (relative or absolute) doses may induce extrapyramidal side-effects, dyskinesia, akathisia, dystonia. These are likely to be particularly severe in children.

In common with other antipsychotics chlorpromazine has been associated with persistent dyskinesia. Tardive dyskinesia may develop in some patients on long term therapy, possibly in relation to total cumulative dose, or may develop after drug therapy has been discontinued. The risk is reported to be greater in elderly patients on high dose therapy.

Characteristic symptoms are rhythmical involuntary movements of the tongue, face, mouth or jaw sometimes accompanied by involuntary movements of the extremities. They persist for many months or even years and, while they gradually disappear in some patients, they appear to be permanent in others.

At the first signs of tardive dyskinesia which may be orofacial dyskinesia the benefit of continued treatment should be carefully assessed against the risk of the development of persistent dyskinesia. Withdrawal of treatment with careful observation of the dyskinesia and psychotic condition has been suggested in order to assess the need for continued neuroleptic therapy and to reveal persisting dyskinesia. Should it be necessary to reinstate treatment, the antipsychotic agent may mask the syndrome. Antiparkinsonian agents have proved of little value in this syndrome.

Endocrine and metabolic reactions:

- Hyperprolactinaemia: amenorrhoea, galactorrhoea, gynaecomastia, impotence, frigidity.
- Thermoregulation disorders.
- Weight gain.
- Hyperglycaemia, changes in glucose tolerance.

Cardiac disorders:

- Tachycardia

- QT interval prolongation.
- Very rare cases of torsades de pointes have been reported.

Skin reactions:

- Allergic skin reactions, rash
- Photosensitivity

Haematological disorders:

- Exceptionally agranulocytosis, regular blood counts are recommended.
- Leukocytopenia.

Immunological disorders:

- Systemic lupus erythematosis has been very rarely reported in patients treated with chlorpromazine. In some cases, positive anti-nuclear antibodies may be seen without evidence of clinical disease.

Miscellaneous:

- Cholestatic jaundice and liver injury, mainly of cholestatic or mixed type, are rarely reported in patients treated with chlorpromazine.
- Neuroleptic malignant syndrome (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Priapism has been very rarely reported in patients treated with chlorpromazine.
- There is a risk of allergic reactions including anaphylactic reactions and bronchospasm owing to the presence of sodium sulfite and disulfite in the formulation.

4.9 Overdose

Symptoms of chlorpromazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. changes, entricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesias may occur.

If the patient is seen sufficiently soon (up to 6 hours) after ingestion of a toxic dose, gastric lavage may be attempted.

Pharmacological induction of emesis is unlikely to be of any use. Activated charcoal should be given. There is no specific antidote. Treatment is supportive.

Generalised vasodilatation may result in circulatory collapse; raising the patient's legs may suffice, in severe cases, volume expansion by intravenous fluids may be needed; infusion should be warmed before administration in order not to aggravate hypothermia.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended; avoid the use of adrenaline.

Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate anti-arrhythmic therapy may be considered. Avoid lignocaine, and, as far as possible, long acting anti-arrhythmic drugs.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10mg) or orphenadrine (20-40 mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam. Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Largactil is a phenothiazine neuroleptic.

The drug is a dopamine inhibitor and inhibits prolactin factor and has alpha-adrenergic blocking and anticholinergic activity as well as being a central nervous system depressant.

5.2 Pharmacokinetic properties

Chlorpromazine is a phenothiazine which is well absorbed but undergoes extensive first pass metabolism in the gut wall and liver with hydroxylation, oxidation and conjugation.

The drug is widely distributed and concentrates in the brain. It is strongly protein bound and eliminated in the urine and intestine as metabolites with a prolonged biphasic half-life of 3 hours and up to 12 days.

5.3 Preclinical safety data

Not relevant

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium sulphite anhydrous (E221)
Sodium metabisulphite powder (E223)
Sodium chloride
Sodium citrate
Water for injections

6.2 Incompatibilities

Largactil injection solutions have a pH of 5.0-6.5; they are incompatible with benzylpenicillin and pentobaritone sodium.

6.3 Shelf Life

5 years

This product should be used immediately after opening.

6.4 Special precautions for storage

Keep in the original container.

6.5 Nature and contents of container

Largactil Injection 2.5% w/v is supplied in a box containing 10 x 2ml Type I glass ampoules.

Pack size: 10 x 2ml Ampoules

6.6 Instructions for use and handling

Single dose container. Discard unused solution.

Discoloured solutions should not be used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 40/18/9

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