Professional information for LARGACTIL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

LARGACTIL 25 tablets

LARGACTIL 100 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LARGACTIL 25: each tablet contains 25 mg chlorpromazine hydrochloride.

LARGACTIL 100: each tablet contains 100 mg chlorpromazine hydrochloride.

Excipients with known effect:

Contains sugar (lactose and sucrose):

LARGACTIL 25 mg contains 79,7 mg lactose and 17,8 mg sucrose per tablet.

LARGACTIL 100 mg contains 318,8 mg lactose and 67,2 mg sucrose per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

LARGACTIL 25: Round, off-white or very pale cream, sugar coated tablets, 4,05 mm thick and 7,4 mm in diameter.

LARGACTIL 100: Round, off-white or very pale cream, sugar coated tablets, 6,3 mm thick and 11,3 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LARGACTIL is used in the management of psychotic conditions to manage excitement, agitation

and other psychomotor disturbances in schizophrenic patients and in the treatment of the manic phase of bipolar disorder.

It is used to control hyperkinetic states and aggression and is sometimes given in other psychiatric conditions for the control of anxiety and tension. LARGACTIL has been used in the alleviation of intractable hiccups.

4.2 Posology and method of administration

Dosage varies with both the individual and the purpose for which the medicine is being used.

Oral:

In most patients oral treatment may be used from the start, commencing with a dosage of 25 to 50 mg three times daily and increasing as necessary; daily doses of 75 mg may be given as a single dose at night.

Lower doses (25 mg every 4 to 6 hours) may be sufficient in some cases.

Intractable hiccups: 25 to 50 mg three or four times daily by mouth for 2 to 3 days.

Elderly and debilitated:

Initial doses of LARGACTIL of one-third to one-half the normal adult dose have been recommended for elderly and debilitated patients; doses should be increased more gradually.

Paediatric population:

This formulation is not suitable for use in children.

4.3 Contraindications

LARGACTIL is contraindicated in patients with:

- Hypersensitivity to chlorpromazine or to any of the ingredients of LARGACTIL (see section 6.1).

- Pre-existing central nervous system (CNS) depression or coma, bone-marrow suppression or phaeochromocytoma.
- Impaired liver, kidney, cardiovascular, cerebrovascular and respiratory function and in those with closed-angle glaucoma, parkinsonism, diabetes mellitus, hyperthyroidism, myasthenia gravis, prostatic hypertrophy or epilepsy.
- Congenital and acquired QT prolongation.

4.4 Special warnings and precautions for use

Epilepsy:

Care is required in epileptic patients receiving anticonvulsant therapy as LARGACTIL may lower the seizure threshold.

QT-interval prolongation:

- Concomitant therapy with other medicines prolonging QT-interval (see section 4.5).
- LARGACTIL may potentiate QT-interval prolongation which increases the risk of onset of serious ventricular dysrhythmias of the Torsades de Pointes type, which is potentially fatal (sudden death). QT-prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalaemia, and congenital or acquired (i.e. medicine 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 LARGACTIL and as deemed necessary during treatment (see section 4.8). LARGACTIL is contraindicated in congenital or acquired QT prolongation (see 4.3).

Stroke:

In randomised clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic medicines, 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 medicines or other populations of patients cannot

be excluded. LARGACTIL should be used with caution in patients with stroke risk factors.

Treatment should be discontinued immediately, and another antipsychotic medicine should be considered as an alternative in the following situations:

Elderly patients with dementia:

Elderly patients with dementia-related psychosis treated with antipsychotic medicines, such as LARGACTIL, are at an increased risk of death.

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 medicines, treatment with conventional antipsychotic medicines may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic medicine as opposed to some characteristic(s) of the patients is not clear.

Severe liver toxicity:

Severe liver toxicity, resulting sometimes in death, has been reported with LARGACTIL use. Patients or caregivers should be instructed to immediately report signs and symptoms, such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a doctor. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8).

Eosinophilia:

The presence of eosinophilia may indicate an allergic reaction to LARGACTIL. A thorough clinical examination and a repeat complete blood count (CBC) with differential count to confirm the presence of eosinophilia should be performed.

Venous thromboembolism:

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic medicines including LARGACTIL. Therefore, LARGACTIL should be used with caution in patients with risk factors for thromboembolism (see section 4.8).

Hyperglycaemia or intolerance to glucose:

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

LARGACTIL tablets also contain sucrose and lactose (see section 6.1) which may also have an effect on the glycaemic control of patients with diabetes mellitus.

CNS depression:

Symptoms of CNS depression may be enhanced by other medicines with CNS-depressant properties including alcohol, general anaesthetics, hypnotics, anxiolytics and sedatives, and opioid anaesthetics.

Effects on the vomiting centre and impaired body temperature regulation:

LARGACTIL's effects on the vomiting centre may mask the symptoms of overdosage of other medicines, or of disorders such as gastrointestinal obstruction. Administration at extremes of temperature may be hazardous since body temperature regulation is impaired by phenothiazines, including LARGACTIL.

Other:

Regular eye examinations are advisable for patients receiving long-term LARGACTIL therapy and avoidance of undue exposure to direct sunlight is recommended.

Haematological parameters should also be monitored periodically.

Withdrawal:

Abrupt withdrawal of LARGACTIL therapy is best avoided.

Lactose/fructose and sucrose intolerance:

LARGACTIL contains lactose and sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption, sucrase-isomaltase insufficiency or fructose intolerance, should not take LARGACTIL tablets.

4.5 Interaction with other medicines and other forms of interaction

CYP1A2 inhibitors:

Administration of LARGACTIL with CYP1A2 inhibitors, in particular strong (such as ciprofloxacin, fluvoxamine, pipemidic acid or zafirlukast) or moderate (such as oral contraceptives or phenylpropanolamine) inhibitors leads to an increase of chlorpromazine plasma concentrations. Therefore patients may experience any LARGACTIL dose-dependent adverse reaction.

Amitriptyline (a CYP2D6 substrate):

Phenothiazines, such as LARGACTIL, are potent inhibitors of CYP2D6. Co-administration of LARGACTIL with amitriptyline, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline. Patients must be monitored for dose-dependent adverse reactions associated with amitriptyline.

The most common interactions encountered with LARGACTIL are adverse effects resulting from concomitant administration of medicines with similar pharmacological actions.

Postural hypotension:

When given with other medicines that produce postural hypotension, dosage adjustments may be necessary. However, it should be noted that LARGACTIL has been reported to reduce the

antihypertensive action of adrenergic receptor blockers.

Antimuscarinic actions and extrapyramidal effects:

As LARGACTIL possesses antimuscarinic actions, it may potentiate the adverse effects of other antimuscarinics, including the antimuscarinic, antiparkinsonian medicines which may be given to treat phenothiazine-induced extrapyramidal effects.

In theory, neuroleptics with dopamine-blocking activity and dopaminergic medicines, such as those used to treat parkinsonism, may be mutually antagonistic.

Metoclopramide:

Concomitant administration of metoclopramide may increase the risk of neuroleptic-induced extrapyramidal effects.

QT- prolonging medicines:

There is an increased risk of dysrhythmias when LARGACTIL is used concomitantly with medicines that prolong the QT-interval, including certain antidysrhythmics, antidepressants and other antipsychotics, some non-sedating antihistamines, and antimalarials; use with diuretics that cause electrolyte imbalance (particularly hypokalaemia) may also have the same effect. There is also an increased risk of dysrhythmias when tricyclic antidepressants are used with antipsychotics that prolong the QT- interval, such as LARGACTIL.

CNS depression:

CNS depression may be enhanced by medicines with similar activity, such as general anaesthetics, hypnotics, anxiolytics and sedatives, opioid anaesthetics and alcohol (see section 4.4).

Antidiabetic medicines:

Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance, the dose of

antidiabetic medicines may need to be increased in diabetic patients. Close monitoring of the blood glucose levels is required and adjustment of the antidiabetic dosage may be required during or after discontinuation of treatment with LARGACTIL.

Antacids:

Antacids, such as magnesium trisilicate and aluminium hydroxide, decreases gastrointestinal absorption of LARGACTIL and should be administered at least 2 hours apart.

Lithium:

Combinations of LARGACTIL and lithium should be used with care. Lithium can reduce plasma concentrations of chlorpromazine and chlorpromazine has also been reported to enhance the excretion of lithium.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of LARGACTIL in pregnant women has not been established. LARGACTIL may prolong labour and should be withheld until the cervix is dilated 3 to 4 cm.

The following effects have been reported (in post-marketing surveillance) in neonates exposed *in utero* to phenothiazines, such as LARGACTIL, during the third trimester of pregnancy:

- various degrees of respiratory disorders ranging from tachypnoea to respiratory distress; bradycardia, and hypotonia, most often when other medicines such as psychotropic or antimuscarinic medicines were co-administered
- signs related to the atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, initial feeding difficulties, abdominal bloating, tachycardia
- neurological disorders such as extrapyramidal symptoms including tremor and hypertonia, somnolence, agitation

Appropriate monitoring and treatment of neonate born to mother receiving LARGACTIL is

recommended.

Studies in animals by oral route have shown reproductive toxicity (dose related embryo fetotoxicity: increased resorptions and dead fetuses). Increased incidence of malformations was observed in mice, but only at doses inducing maternal mortality.

Data from available epidemiological studies in children exposed *in utero* to LARGACTIL cannot exclude the risk of congenital malformations and neurodevelopmental disorders.
Therefore, the use of LARGACTIL is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation:

LARGACTIL may be excreted in milk, therefore it should not be used in lactating mothers.

Fertility:

In humans, because of the interaction with dopamine receptors, LARGACTIL may cause hyperprolactinaemia which can be associated with impaired fertility in women. In men, data on consequences of hyperprolactinaemia are insufficient with regard to fertility.

4.7 Effects on ability to drive and use machines

The sedative effects of LARGACTIL are marked; patients should not drive or operate machinery.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent: haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, leucocytosis and a potentially fatal agranulocytosis (they may be manifestations of a hypersensitivity reaction).

Most cases of agranulocytosis have occurred within 4 to 10 weeks of starting treatment and

symptoms such as sore throat or fever should be watched for and white cell counts instituted should they appear.

Frequency unknown: mild leucopenia (has been stated to occur in up to 30 % of patients on prolonged, high dosage LARGACTIL), thrombocytopenia

Endocrine disorders:

Frequency unknown: amenorrhoea, hyperprolactinaemia, galactorrhoea, gynaecomastia

Metabolism and nutrition disorders:

Frequency unknown: hyperglycaemia and intolerance to glucose (see section 4.4), hypertriglyceridaemia, hyponatraemia, inappropriate antidiuretic hormone secretion, weight gain

Psychiatric disorders:

Frequent: drowsiness

Less frequent: catatonic-like states, insomnia, nightmares and depression

Frequency unknown: delirium, agitation

Nervous system disorders:

Frequency unknown: extrapyramidal dysfunction (including acute dystonia, a parkinsonism-like syndrome, and akathisia; late effects include tardive dyskinesia and perioral tremor.); neuroleptic malignant syndrome (clinical features include hyperthermia, severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction, and altered levels of consciousness; skeletal muscle damage may occur and resulting myoglobinuria may lead to renal failure.); electroencephalogram (EEG) changes and convulsions

Eye disorders:

Less frequent: pigment retinopathy

Frequency unknown: deposition of pigment in the eyes (with prolonged therapy); corneal and

lens opacities, miosis, blurred vision, mydriasis

Cardiac disorders:

Frequent: hypotension (usually postural)

Less frequent: cardiac dysrhythmias

Frequency unknown: tachycardia, electrocardiographic changes (particularly QT-interval prolongation), sudden death (possible causes include cardiac dysrhythmias (see sections 4.3 and 4.4) or aspiration and asphyxia due to suppression of the cough and gag reflexes), unexplained sudden death

Vascular disorders:

Frequency unknown: venous thromboembolism, pulmonary embolism (sometimes fatal) and deep vein thrombosis (see section 4.4)

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: nasal congestion

Gastrointestinal disorders:

Frequency unknown: ischaemic colitis, intestinal obstruction, gastrointestinal necrosis, necrotising colitis (sometimes fatal), intestinal perforation (sometimes fatal), dry mouth, constipation

Hepatobiliary disorders:

Frequency unknown: abnormal liver function tests, cholestatic jaundice; hepatocellular, cholestatic and mixed liver injury, sometimes resulting in death (see section 4.4)

Skin and subcutaneous tissue disorders:

Frequency unknown: hypersensitivity reactions include angioedema, urticaria, exfoliative dermatitis, erythema multiforme and contact sensitivity, deposition of pigment in the skin (with

prolonged therapy), systemic lupus erythematosus (in some cases, positive anti-nuclear antibodies may be seen without evidence of clinical disease), photosensitivity reactions

Renal and urinary tract disorders:

Frequency unknown: difficulty with micturition

Reproductive system and breast disorders:

Frequency unknown: inhibition of ejaculation, impotence, priapism

General disorders and administration site conditions:

Frequency unknown: withdrawal symptoms after prolonged use and abrupt withdrawal, impaired body temperature regulation (hypo- or hyperthermia)

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of LARGACTIL is important. It allows continued monitoring of the benefit/risk balance of LARGACTIL. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256-3700 (tel), or
- SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the event of an overdose convulsions and other side effects listed may occur. See section 4.8 above.

Following recent ingestion of an overdose of LARGACTIL activated charcoal should be administered. Patients should be managed with intensive symptomatic and supportive therapy.

Dialysis is of little or no value in poisoning by LARGACTIL.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class:

A 2.6.1 Phenothiazines and their derivatives

Pharmacotherapeutic group: Antipsychotic drugs

ATC code: N05AA01

Chlorpromazine is a phenothiazine and has pharmacological activity affecting both the autonomic and central nervous systems.

It is a dopamine-receptor blocker and has a peripheral alpha-adrenergic blocking action.

5.2 Pharmacokinetic properties

Chlorpromazine is erratically, absorbed from the gastrointestinal tract and peak plasma concentrations occur 2 to 4 hours after ingestion.

Chlorpromazine is about 95 to 98 % bound to plasma proteins. It is widely distributed in the body. It crosses the blood-brain barrier and achieves higher concentrations in the brain, lungs and other tissue with a high blood supply. Chlorpromazine and its metabolites also cross the placenta and are distributed into breast milk.

Chlorpromazine is extensively metabolised in the liver, through CYP2D6.

Although the plasma half-life of chlorpromazine itself has been reported to be about 30 hours, elimination of the metabolites may be very prolonged. Chlorpromazine is excreted in the urine and bile.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia powder (E414)

Carnauba wax (E 903)

Dextrin white technical

Gelatin (E441)

Kaolin light

Lactose

Magnesium stearate (E572)

Purified talc (e553b)

Polyethylene glycol (E1521)

Polyvinylpyrrolidone (E1201)

Stearic acid (E570)

Sodium metabisulphite (E223)

Sucrose (E473)

Titanium dioxide (E171).

LARGACTIL 25:

Vinac B7.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

Tablets of 25 mg and 100 mg in containers of 28, 50, 56, 84 and 500.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand

South Africa

1685

8. REGISTRATION NUMBERS

LARGACTIL 25: B511 (Act 101/1965)

LARGACTIL 100: B513 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Old Medicine (Act 101 of 1965).

10. DATE OF REVISION OF THE TEXT

14 October 2022