SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

LANTANON® 10 mg Tablets

LANTANON® 30 mg Tablets

COMPOSITION

Each LANTANON 10 mg film-coated tablet contains 10 mg mianserin hydrochloride.

Each LANTANON 30 mg film-coated tablet contains 30 mg mianserin hydrochloride.

Lantanon Tablets are sugar free.

Inactive ingredients: Potato starch, Aerosil, magnesium stearate, methyl cellulose, calcium hydrogen phosphate.

Film-coating solution: macrogol, titanium dioxide, hypromellose.

PHARMACOLOGICAL CLASSIFICATION

A.1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTION

Pharmacodynamics

Mianserin is a tetracyclic antidepressant. Its active substance belongs to the piperazino-azepine group of compounds. It possesses sedative properties. Mianserin is an antagonist at central presynaptic α_2-adrenoreceptors and antagonist at 5-HT_{2a}, 5-HT_{2c} and 5-HT_3 receptors.

Pharmacokinetics

Absorption

After oral administration of LANTANON the active constituent, mianserin is rapidly and well absorbed, reaching peak plasma levels within 3 hours. The bioavailability is approximately 20 %. Steady-state plasma levels are reached within 6 days.

Distribution

Binding of mianserin to plasma proteins is approximately 95 %.

Metabolism

Major pathways of biotransformation are demethylation and oxidation, followed by conjugation.

Mianserin is extensively metabolised.

Elimination

Mianserin is eliminated via the urine and faeces within 7 to 9 days. The half-life of elimination is 21 to 61 hours and is sufficient to justify once-a-day dosing.

INDICATIONS

For relief of symptoms of depression in those cases of depressive illness where medicinal therapy is indicated.

CONTRAINDICATIONS

- Mania.
- Severe liver disease.
- Hypersensitivity to mianserin or to any of the inactive ingredients.

- Concomitant use of mianserin with monoamine oxidase (MAO) inhibitors or within 2 weeks of cessation of therapy with MAO inhibitors (see **INTERACTIONS**).
- Children and adolescents under 18 years of age.

WARNINGS AND SPECIAL PRECAUTIONS

- **Use in children and adolescents under 18 years of age**

  LANTANON should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

- **Suicide/suicidal thoughts or clinical worsening**

  Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs.

As improvement may not occur during the first few weeks of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants, compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany therapy with

antidepressants such as LANTANON, especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of LANTANON tablets should be given to the patient.

LANTANON may precipitate hypomania in susceptible subjects with bipolar depressive illness. In such a case treatment with LANTANON should be withdrawn.

Treatment should be withdrawn if jaundice occurs.

Treatment should be discontinued if convulsions occur.

Bone-marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with LANTANON. These reactions have occurred most commonly after 4 to 6 weeks of treatment and were generally reversible on stopping treatment. If a patient shows fever, sore throat, stomatitis or other signs of infection, a full blood count should be obtained. This adverse reaction has been observed in all age groups but appears to be more common in the elderly.

When treating patients with diabetes or cardiac disease, hepatic or renal insufficiency, normal precautions should be exercised and the dosages of any concomitant therapy kept under review.

QT prolongation and ventricular arrhythmias (including Torsades de Pointes) have been reported during the post-marketing use of LANTANON. LANTANON should be used with

caution in patients with risk factors for QT prolongation/TdP including congenital long QT syndrome, age > 65 years, female sex, structural heart disease/left ventricular (LV) dysfunction, renal or hepatic disease, use of medicines that inhibit the metabolism of LANTANON, and the concomitant use of other QTc prolonging medicines. Hypokalaemia and hypomagnesaemia should be corrected prior to treatment. Consideration should be given to stop LANTANON treatment or reducing the dose if the QTc interval is > 500ms or increases by > 60ms.

Patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy should also be monitored even though anticholinergic side effects are not anticipated with LANTANON therapy. LANTANON should be used with caution in patients with cardiovascular disorders, such as ischaemic heart disease.

Effects on Ability to Drive and Use Machines

LANTANON may impair psychomotor performance for the first few days of treatment. In general, depressed patients treated with LANTANON should avoid the performance of potentially dangerous tasks such as driving a motor vehicle or operating machinery.

INTERACTIONS

LANTANON may potentiate the central nervous system depressant action of alcohol and patients should be advised to avoid taking alcohol during treatment.

LANTANON should not be administered concomitantly with MAO-inhibitors or within 2 weeks after discontinuation of MAO-inhibitor therapy. In the opposite way about 2 weeks should pass before patients treated with LANTANON should be treated with MAO-inhibitors (see **CONTRAINDICATIONS**).

LANTANON does not interact with bethanidine, clonidine, methyldopa or propranolol (either alone or in combination with hydralazine). Nevertheless, it is recommended to monitor the blood pressure of those patients who are concomitantly treated with antihypertensive medicines.

Concomitant treatment with antiepileptic medicines that are CYP3A4 inducers (like phenytoin and carbamazepine), can result in reduced plasma levels of mianserin. Dose adjustment should be considered when concomitant treatment with these medicines is initiated or discontinued.

LANTANON may affect the metabolism of coumarin derivatives like e.g. warfarin, necessitating supervision.

The risk of QT prolongation and/or ventricular arrhythmias (e.g. Torsades de Pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the product information of other medicines administered for information on their effects on the QTc interval.

PREGNANCY AND LACTATION

Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Adults: Treatment should begin with 30 to 40 mg daily, taken in the evening and dosage should be adjusted according to the clinical response. The effective dose usually lies between 30 mg and 90 mg (mostly 60 mg) daily.

Elderly: Not more than 30 mg initially. The dose should be slowly increased under close supervision. A lower than the normal maintenance dose may be sufficient for a satisfactory clinical response.

LANTANON should not be used in children and adolescents under the age of 18 years (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Administration

The tablets should be swallowed without chewing.

SIDE EFFECTS

System organ class	**Frequency estimate of side effects** **Frequency Unknown**
Blood and the lymphatic system disorders	Blood dyscrasia, usually presenting as granulocytopenia or agranulocytosis, see **WARNINGS AND SPECIAL PRECAUTIONS**.
Metabolism and nutrition disorders	Weight increase
Psychiatric disorders	Hypomania
Nervous system disorders	Sedation (occurring at initiating of treatment and decreasing as treatment continues. Note that dose reduction generally does not lead to less sedation but can jeopardise antidepressant efficacy), convulsions, hyperkinesia (restless legs), neuroleptic malignant syndrome (NMS), dizziness
Eye disorders	Dilated pupils, constricted pupils
Cardiac disorders	Bradycardia (after the initial dose) Electrocardiogram QT prolonged

	Torsade de pointes
Vascular disorders	Hypotension
Gastrointestinal disorders	Vomiting
Hepatobiliary disorders	Elevated liver enzymes, jaundice, hepatitis, hepatic function abnormal
Skin and subcutaneous tissue disorders	Exanthema
Musculoskeletal, connective tissue and bone disorders	Arthralgia
Reproductive system and breast disorders	Gynaecomastia
General disorders and administrative site conditions	Oedema, ataxia

Cases of suicidal ideation and suicidal behaviour have been reported during LANTANON treatment or early after treatment discontinuation (see **WARNINGS AND SPECIAL PRECAUTIONS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of acute overdosage are prolonged sedation. Cardiac dysrhythmias, convulsions, severe hypotension and respiratory depression occur. Electrocardiogram QT prolonged and Torsade de Pointes has also been reported. ECG monitoring should be undertaken. There is no specific antidote. Treatment is by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

IDENTIFICATION

LANTANON 10 mg: White, round and biconvex film-coated tablets, CT above 4 on one side and Organon on the reverse side.

LANTANON 30 mg: White, oval and biconvex film-coated tablets, coded CT above 7 on both sides of the score on one side and Organon on the reverse side.

PRESENTATION

LANTANON 10 mg: Press-through strips with 30 and 90 tablets.

LANTANON 30 mg: Press-through strips with 40 tablets (4 x 10 tablets).

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Protect from light.

Keep out of reach of children.

REGISTRATION NUMBERS

LANTANON 10 mg: J/1.2/64

LANTANON 30 mg: N/1.2/180

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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