AUSTRALIAN PRODUCT INFORMATION

LUMIN®

(mianserin hydrochloride) tablets

1 NAME OF THE MEDICINE

Mianserin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LUMIN tablet contains either 10 mg or 20 mg of mianserin hydrochloride as the active ingredient.

Excipients with known effect: trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

LUMIN 10 mg tablets: 6 mm normal convex white film coated tablet marked MI 10 on one side, G on the reverse.
LUMIN 20 mg tablets: 7 mm normal convex white film coated tablet marked MI 20 on one side, G on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of major depression.

4.2 DOSE AND METHOD OF ADMINISTRATION

LUMIN tablets should be taken orally between meals, preferably with a little fluid, and swallowed without chewing.

Use in Children and Adolescents (< 18 years of age)

LUMIN should not be used in children and adolescents under the age of 18 years (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adults

The initial dosage of LUMIN should be judged individually. It is recommended that treatment begin with a daily dose of 30 mg given in three divided doses or as a single bedtime dose and be adjusted weekly in the light of the clinical response. The effective daily dose for adult patients usually lies between 30 mg and 90 mg (average 60 mg) in divided doses or as a single bedtime dose. A maximum daily dose of 120 mg should not be exceeded. It is often advantageous to maintain antidepressant treatment for several months after initial clinical improvement has occurred.

Elderly

Initially, not more than 30 mg daily and increased slowly under close supervision. A reduced dose may also be required for maintenance, as hepatic, renal or cardiovascular function may be impaired.
Pharmacokinetic studies of mianserin in the elderly patient suggest a longer half-life and slower metabolic clearance. This implies that a single night-time dose of mianserin hydrochloride should be preferred to divided doses in the elderly patient.

4.3 CONTRAINDICATIONS

- Hypersensitivity to mianserin or any of the excipients listed under Section 6.1 LIST OF EXCIPIENTS
- Mania

- Severe liver disease
- Concomitant use of mianserin with monoamine oxidase (MAO) inhibitors (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical Worsening and Suicide Risk

The risk of suicidality (suicidal ideation and suicidal behaviours) is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients; 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. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and/or behaviours whether or not they are taking antidepressant medication, and this risk may persist until significant remission occurs. Suicide is a known risk in depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation or behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analysis of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increased the risk of suicidal ideation and/or behaviours in children, adolescents, and young adults (aged 18-24 years) with major depressive disorder (MDD) and other psychiatric disorders during the initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials (4 to 16 weeks) of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in the risk of suicidality among drugs, but a tendency towards an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across different indications, with the highest incidence in MDD trials. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications.

No suicides occurred in any of the paediatric trials. There were few suicides in the adult trials, but the number was not sufficient to reach any conclusion about the effect of antidepressants on suicide. It is unknown whether suicidality risk extends to longer-term use, i.e. beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidality has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for LUMIN should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression. When the depressive phase of bipolar is being treated, it can transform into the manic phase. Patients should be closely monitored and mianserin discontinued in any patient with signs or symptoms of a mixed/manic episode.

Effects on the blood

Bone marrow depression, usually presenting as neutropenia, agranulocytosis and thrombocytopenia have been reported during treatment with mianserin hydrochloride. These reactions have occurred most commonly after 4 to 6 weeks of treatment. Patients complaining of sore throat, stomatitis, fever, malaise, flu-like symptoms or other signs of infection should discontinue treatment with mianserin, and a full blood count should be obtained. Elderly patients who have a white blood cell disorder should have a full blood count performed every 4 weeks during the first 3 months of treatment.

Effects on the cardiovascular system

Although mianserin hydrochloride at therapeutic doses has not been shown to have cardiotoxic effects, caution should be exercised in treating patients with cardiac impairment (e.g. heart block, recent myocardial infarction and unstable heart disease) who should be monitored carefully.

QT prolongation and ventricular arrhythmias (including Torsades de Pointes) have been reported during the post-marketing use of mianserin hydrochloride (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Mianserin hydrochloride 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 mianserin hydrochloride, and the concomitant use of other QTc prolonging medicines (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment. Consideration should be given to stop mianserin hydrochloride treatment or reducing the dose if the QTc interval is >500ms or increases by >60ms.

Effects on motor co-ordination

Mianserin hydrochloride, especially in the first days of treatment, may impair concentration and psychomotor skills and hence ability to drive or engage in any activity requiring alertness may be impaired. This risk is increased if alcohol is taken concomitantly with mianserin hydrochloride.

Effects on the eye

Patients with narrow angle glaucoma should be monitored even though anticholinergic side effects are not expected with LUMIN therapy.

Epileptogenic effect

As clinical experience is lacking in patients suffering from epilepsy, care must be exercised. Mianserin hydrochloride may lower the convulsive threshold in such patients. It may therefore be necessary to adjust the dose of anticonvulsants if administered. Convulsions have also been reported in nonepileptic patients. If convulsions occur, LUMIN therapy should be discontinued. However, mianserin products including LUMIN should be avoided, if possible, in patients with epilepsy.

Effects on the prostate

Patients with symptoms suggestive of prostatic hypertrophy should be monitored even though anticholinergic side effects are not expected with LUMIN.

Psychiatric effects

Mianserin hydrochloride, like other antidepressants, may precipitate hypomania in susceptible subjects with bipolar depressive illness. In such a case treatment with mianserin should be withdrawn. The possibility of the depressed patient attempting suicide should be borne in mind, and large amounts of the drug should not be held by the patient.

Effects on metabolism

Slight alterations of the glucose tolerance curve and insulin levels have been observed in some patients with diabetes mellitus, who were treated with mianserin hydrochloride. Therefore, in such patients regular monitoring of blood glucose levels is advisable.

Effects on surgery

Clinicians should inform anaesthetists if surgery becomes necessary during mianserin hydrochloride treatment.

Use in Hepatic and Renal Impairment

Depressed patients suffering from liver or renal insufficiency should be carefully monitored, because of the possibility of increases in serum-derived liver enzyme levels (mainly ALT) and impaired metabolism or excretion. If jaundice occurs, LUMIN should be discontinued.

Use in the Elderly

No data available.

Paediatric Use

The safety and efficacy of LUMIN for the treatment of depression or other psychiatric disorders in children and adolescents aged less than 18 years has not been satisfactorily established. LUMIN should not be used in this age group for the treatment of depression or other psychiatric disorders. (See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Clinical Worsening And Suicide Risk).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant use of barbiturates with mianserin hydrochloride is not recommended as there may be additive central depressant effects.

Mianserin hydrochloride should not be administered concomitantly with monoamine oxidase inhibitors (such as moclobemide, tranylcypromine and linezolid) or within two weeks after MAOIs have been discontinued. In the opposite way about two weeks should pass before patients treated with mianserin should be treated with MAO inhibitors.

Mianserin hydrochloride may affect the metabolism of coumarin derivatives such as warfarin. Patients receiving warfarin therapy should receive coagulation monitoring when LUMIN is initiated or stopped.

It has been shown that alcohol potentiates the impairment of psychomotor skills especially in the initial period of treatment. Patients should be advised to avoid taking alcohol during treatment.

Although there is evidence that the tyramine uptake into peripheral noradrenergic neurones in depressed patients receiving mianserin hydrochloride is not inhibited, it is nevertheless advisable to check the blood pressure regularly in those patients who are concomitantly treated with antihypertensives.

Mianserin hydrochloride has been used with benzodiazepines without apparent ill effect.

Concomitant treatment with antiepileptic drugs that are CYP 3A4 inducers (like phenytoin and carbamazepine) can result in reduced plasma levels of mianserin. Dose adjustment should be considered when concomitant treatment with these drugs is initiated or discontinued.

Phenytoin levels need to be monitored.

The risk of QTc 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 anti-psychotics and antibiotics). Please check the product information of other medicines administered for information on their effects on the QTc interval.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B2

There is limited experience of the effects of mianserin hydrochloride in human pregnancy and therefore it should not be given to pregnant women or those likely to become pregnant unless the expected benefit outweighs the potential risk.

Available data on the few studies conducted in animals show no evidence of an increase of occurrence of fetal damage, however, the number of implantation sites were significantly reduced in a rat fertility study in which dams were dosed at greater than 3 mg/kg/day. There is only limited evidence of safety in pregnancy.

Use in Lactation

It is not known whether mianserin hydrochloride is excreted in human milk nor whether it has a harmful effect on newborns. Therefore, it is recommended that mianserin not be given to nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting frequencies are described as follows, according to CIOMS Working Group III.
Very common: > 10%; common: 1 to 10%; uncommon: 0.1 to 1%; rare: 0.01 to 0.1%; very rare: < 0.01%; frequency not known.

Blood and the lymphatic system disorders.

Very rare: blood dyscrasias.

Investigations.
Uncommon: weight gain.

General disorders.
Rare: oedema.

Musculoskeletal and connective tissue disorders.
Rare: arthralgia/arthritis.

Skin and subcutaneous tissue disorders.
Rare: exanthema.

Nervous system disorders.
Common: sedation (primarily at initiation of treatment).
Very rare: convulsions, hyperkinesia (restless legs), neuroleptic malignant syndrome.

Psychiatric disorders.
Rare: hypomania.

Vascular disorders.
Rare: hypotension (postural).

Cardiac disorders.
Very rare: bradycardia.
Frequency not known: Electrocardiogram, QT prolonged, Torsade de Pointes.

Hepato-biliary disorders.
Rare: disturbances of liver function including jaundice, hepatitis.
Frequency not known: elevated liver enzymes, hepatic function abnormal.

Serious or life-threatening reactions

Blood and the lymphatic system disorders.

Very rare: bone marrow depression resulting in neutropenia, granulocytopenia, leukopenia, agranulocytosis, pancytopenia, thrombocytopenia, anaemia (aplastic, B12 deficiency, haemolytic, hypoplastic, normocytic, sideroblastic).

Cardiac disorders.
Very rare: cardiac arrest, cardiac failure.
These reactions necessitate immediate withdrawal of LUMIN therapy and are reversible on stopping treatment.
If jaundice, hypomania or convulsions occur at therapeutic dosages, then treatment should be withdrawn.

Other reactions

The following adverse events have been reported in association with mianserin hydrochloride use. A causal relationship has not been established.

Gastrointestinal disorders:
Very common: dry mouth, constipation.

Nervous system disorders.
Common: tremor, headache.
Rare/very rare: paraesthesia.

Respiratory, thoracic and mediastinal disorders.
Rare/very rare: nasal congestion.

Eye disorders.
Rare/very rare: vision abnormality, diplopia.

Reproductive system and breast disorders.
Rare/very rare: gynaecomastia, impotence.

Musculoskeletal and connective tissue disorders.
Rare/very rare: myalgia.

Skin and subcutaneous tissue disorders.
Rare/very rare: pruritus.

Vascular disorders.
Rare/very rare: hypertension.

Cardiac disorders.
Rare/very rare: tachycardia.

Ear and labyrinth disorders.
Rare/very rare: tinnitus.

Psychiatric disorders.
Rare/very rare: confusion, agitation.
Cases of suicidal ideation and suicidal behaviours have been reported during mianserin therapy or early after treatment discontinuation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

More common reactions

More Common Reactions (from clinical trials)		
Reaction	**% in first week***	**% on maintenance therapy***
Tiredness, lethargy and drowsiness	34%	5 - 10%
Dry mouth	33%	10 - 20%
Dizziness, faintness, weakness, vertigo	> 5%	5%
Drug related withdrawal in clinical trials	-	8% **
Tremor	-	5% **
Headache	-	6% **

* Percentages are estimates from clinical trials; not corrected for baseline incidence.
** These figures represent overall incidence.
Note: Anticholinergic type side effects are less frequent than with the tricyclic antidepressants and may be difficult to distinguish from symptoms of depression.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The toxic effects of mianserin hydrochloride are different from those of the tricyclics and there is no specific antidote.

Symptoms

Symptoms of acute overdose are generally confined to prolonged sedation. Cardiac arrhythmias, convulsions, severe hypotension and respiratory depression occur rarely. Electrocardiogram QTc prolonged and Torsade de Pointes has also been reported. ECG monitoring should be undertaken. There is no specific antidote.

Treatment

Treatment is by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mianserin belongs to the piperazino-azepine group of compounds which are chemically not related to the tricyclic antidepressants (TCAs). Its structure lacks the basic side chain which is considered to be responsible for the anticholinergic activity of the TCAs. It increases central noradrenergic neurotransmission by α_2-autoreceptor blockade and noradrenaline (norepinephrine) reuptake inhibition. In addition, interactions with serotonin receptors in the central nervous system have been found. Human pharmaco-electroencephalographic (EEG) studies have confirmed the antidepressant profile of mianserin hydrochloride.

The antidepressant efficacy of mianserin hydrochloride has been demonstrated in placebo controlled trials and has been shown to be similar to other currently used antidepressants. Moreover, it possesses anxiolytic and sleep improving properties which are of value in treating patients with anxiety or sleep disturbances associated with depressive illness. The histamine H_1- and α_1-antagonistic activity of mianserin hydrochloride is thought to be responsible for its sedative properties.

Mianserin hydrochloride is well tolerated, also by the elderly and by patients with cardiovascular disease. At therapeutically effective doses mianserin hydrochloride has virtually no anticholinergic activity and has practically no effect on the cardiovascular system. As compared to the TCAs, it causes less cardiotoxic effects on overdose. It does not antagonise the action of sympathicomimetic agents and antihypertensive drugs which interact with adrenergic receptors (e.g. bethanidine) or α_2-receptors (e.g. clonidine, methyldopa).

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, mianserin hydrochloride is rapidly and well absorbed reaching peak plasma levels within 3 hours. The bioavailability is approximately 20%. Binding of mianserin to plasma proteins is approximately 95%. The half-life of elimination (21 - 61 hours) is sufficient to justify once-a-day dosing. Steady-state plasma levels are reached within six days. Mianserin is extensively metabolised and eliminated via the urine and faeces within seven to nine days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Pregelatinised maize starch, colloidal anhydrous silica, microcrystalline cellulose, calcium hydrogen phosphate, magnesium stearate, carnauba wax, Opadry Complete film coating system White Y-1-7000 (ARTG PI No: 1475).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al

Pack sizes: 50 tablets

Australian Register of Therapeutic Goods (ARTG)

AUST R 55272 – LUMIN 10 Mianserin hydrochloride 10mg tablet blister pack

AUST R 55273 – LUMIN 20 Mianserin hydrochloride 20mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

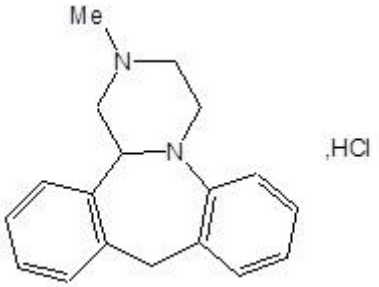
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Mianserin belongs to the tetracyclic series of antidepressant compounds, the piperazinoazepines. These are chemically different from the common tricyclic antidepressants.

Mianserin hydrochloride is an odourless, creamy white, crystalline powder that is soluble in water, ethanol, methanol and chloroform.

Chemical Structure



Chemical name	:	1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c,f]pyrazino[1,2-a]azepine monohydrochloride			
Molecular formula	:	$C_{18}H_{20}N_2HCl$	Molecular weight	:	300.8

CAS Number

21535-47-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

20/05/1996

10 DATE OF REVISION

26/03/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Move chemical details to Section 6.7
6.5	Add AUST R details
8	Update to sponsor details

LUMIN_pi\Apr24/00