Name of the Medicine

The active ingredient of Lumin tablets is mianserin hydrochloride.

The chemical name of mianserin hydrochloride is 1,2,3,4,10,14b-hexahydro-2-methyl dibenzo[c,f]pyrazino[1,2-a]azepine monohydrochloride. Its structural formula is:

![Structural formula of mianserin hydrochloride]

Molecular formula: $\text{C}_{18}\text{H}_{20}\text{N}_{2}\text{HCl}$
Molecular weight: 300.8
CAS Registry No.: 21535-47-7

Description

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

Each Lumin 10 tablet contains 10 mg of mianserin hydrochloride and each Lumin 20 tablet contains 20 mg of mianserin hydrochloride.

The tablets also contain the following inactive excipients: pregelatinised maize starch, colloidal anhydrous silica, microcrystalline cellulose, calcium hydrogen phosphate anhydrous, magnesium stearate, Opadry White Y-1-7000 and carnauba wax.

Pharmacology

Mianserin belongs to the piperazinoazepine 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 $\alpha_2$-autoreceptor blockade and noradrenaline 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 H1- and α1-antagonistic activity of mianserin hydrochloride is thought to be responsible for its sedative properties.

Mianserin hydrochloride is well tolerated, including 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 sympathomimetic agents and antihypertensive drugs that interact with adrenergic receptors (e.g. bethanidine) or α2-receptors (e.g. clonidine, methyldopa).

**Pharmacokinetics**

Mianserin hydrochloride is rapidly absorbed after oral administration. Peak plasma levels are reached within 3 hours. The bioavailability is approximately 20%. Approximately 95% of the drug is bound to plasma proteins.

The half-life of elimination (approximately 20 hours) is sufficient to justify once daily 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.

Mianserin is a substrate for the polymorphic cytochrome P450 2D6 (CYP2D6) enzyme and thus its metabolism may be subject to patient variation. Care should therefore be taken when prescribing mianserin to ensure that the dose is individualised for each patient (see **Dosage and Administration**).

**Indications**

For the treatment of major depression.

**Contraindications**

Hypersensitivity to mianserin hydrochloride or any inactive ingredient

Mania

Severe hepatic disease.

**Precautions**

**Clinical Worsening and Suicide Risk associated with Psychiatric Disorders**

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 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/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 analysis 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 antidepressants 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, ie., 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 suicidal impulses 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.

**Effects on the blood**

Neutropenia, agranulocytosis and thrombocytopenia have been reported during treatment with mianserin hydrochloride. These reactions have most commonly occurred after 4 to 6 weeks of treatment. A full blood count should be performed in patients complaining of sore throat, fever, stomatitis, malaise, flu-like symptoms or other signs of infection. Mianserin hydrochloride should be discontinued if neutropenia is observed in the full blood count. Elderly patients with a history of white blood cell disorders should have a full blood count examination every 4 weeks during the first 3 months of treatment.

**Impairment of motor co-ordination**

Mianserin hydrochloride, especially in the first days of treatment, may impair concentration and psychomotor skills and hence the 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.

**Psychiatric effects**

Mianserin hydrochloride, like other antidepressants, may precipitate hypomania in susceptible individuals with bipolar depressive illness. In such a case, mianserin treatment 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 the cardiovascular system**

Although mianserin hydrochloride at therapeutic doses has not been shown to have cardiotoxic effects, caution and careful monitoring 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.

**Effects on the eye**

Patients with narrow angle glaucoma should be monitored, even though anticholinergic side effects are not usually 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 anti-convulsants 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.

**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 the liver and renal systems

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.

Effects on surgery

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

Carcinogenicity/Mutagenicity

No information is available.

Use in Pregnancy (Category B2)

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

Data available from the few studies conducted in animals show no evidence of an increase of occurrence of foetal damage. However, the number of implantation sites was 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 newborn infants. Therefore, it is recommended that mianserin not be given to nursing mothers.

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

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 Precautions – Clinical Worsening and Suicide Risk associated with Psychiatric Disorders)

Interactions with Other Medicines

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

Mianserin hydrochloride should not be used in combination with monoamine oxidase inhibitors (MAOIs) as the results of this combination have not been investigated. Mianserin hydrochloride should not be commenced until two weeks after MAOIs have been stopped. Similarly, a MAOI should not be commenced until one week after mianserin hydrochloride has been stopped.

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.
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.

Phenytoin levels need to be monitored.

**Adverse 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%.

**Blood and 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.

**Hepato-biliary disorders.** Rare: disturbances of liver function including jaundice.

**Serious or life-threatening reactions**

**Blood and lymphatic system disorders.** Very rare: bone marrow depression resulting in neutropenia, granulocytopenia, leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, anaemia (aplastic, vitamin 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 use of mianserin hydrochloride. 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 and agitation.

More common reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>% in first week*</th>
<th>% on maintenance therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness, lethargy and drowsiness</td>
<td>34%</td>
<td>5 - 10%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>33%</td>
<td>10 - 20%</td>
</tr>
<tr>
<td>Dizziness, faintness, weakness, vertigo</td>
<td>&gt; 5%</td>
<td>5%</td>
</tr>
<tr>
<td>Drug related withdrawal in clinical trials</td>
<td>-</td>
<td>8% **</td>
</tr>
<tr>
<td>Tremor</td>
<td>-</td>
<td>5% **</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>6% **</td>
</tr>
</tbody>
</table>

* 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.

Dosage and Administration

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

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 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.

**Children and Adolescents (< 18 years of age)**

Lumin is not recommended for use in children and adolescents less than 18 years of age as there is no clinical experience in this age group (see **Precautions**).

**Overdosage**

As with other antidepressants, combination overdoses of mianserin hydrochloride and other antidepressants, alcohol and other drugs (e.g. barbiturates) can be life threatening. 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. There is no specific antidote.

**Treatment**

Careful monitoring of vital functions, including ECG, should be carried out and supportive measures instituted as necessary.

**Presentation and Storage Conditions**

**Lumin 10**, 10 mg tablet: white, film coated, normal convex, marked MI 10 on one side, G on reverse; 50’s.

**Lumin 20**, 20 mg tablet: white, film coated, normal convex, marked MI 20 on one side, G on reverse; 50’s.

Store below 30ºC.

**Poison Schedule of the Medicine**

S4 (Prescription Only Medicine)

**Name and Address of the Sponsor**

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Date of Approval

Approved by the Therapeutic Goods Administration on 7 April 2005.

Date of most recent amendment: 18 January 2008.