Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mianserin 10 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg mianserin hydrochloride.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet. (Tablet)

White, circular, film-coated biconvex tablets, about 6 mm in diameter marked ‘MI 10’ on one face and ‘G’ on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of primary depressive illness, (e.g. endogenous depression, reactive depression, involutional melancholia, depression in association with physical complaints).

In those cases where marked anxiety or insomnia is a predominant feature of depressive illness, mianserin may be effective without concomitant tranquillizing treatment.

4.2 Posology and method of administration

Oral. The tablets should be swallowed whole without chewing, preferably with some fluid.

Adults

Clinical treatment should be started with 30 mg daily and the dosage adjusted by the clinical reaction. The daily effective dose in adults usually lies between 30 to 90 mg. The total daily dose may be given either as a single night-time dose or divided into three sub-doses.

Elderly Patients

An initial dose of 30 mg daily may be slowly increased under close supervision. Mianserin has a longer half life and slower metabolite clearance in the elderly.

Children and adolescents

Mianserin should not be used in the treatment of children and adolescents under the age of 18 years (See section 4.4 Special Warnings and Precutions for Use).

4.3 Contraindications

Mania, use during pregnancy and lactation, use in children and severe liver disease.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age :
Mianserin should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), 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. If, based on clinical need, a decision to treat is nevertheless taken, the patients should be carefully monitored for the appearance of suicidal symptoms. 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 or more 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 antidepressant drugs in adult patients with psychiatric disorders showed and 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 drug therapy especially in early tratment 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.

The drowsiness associated with Mianserin may be potentiated by alcohol.

This drug may precipitate hypomania in susceptible subjects with bipolar affective illness.

Care is necessary for use in patients with severe liver or kidney dysfunction, with cardiac insufficiency or with diabetes mellitus.

Bone marrow depression usually presenting as granulocytopenia or agranulocytosis has been reported during treatment with mianserin. These reactions have occurred most commonly after 4-6 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 groups, but appears to be more common in the elderly.

Patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy should be monitored even though anti-cholinergic side effects are not anticipated with mianserin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

The drug should not be administered concomitantly with or within 2 weeks of cessation of therapy with monoamine oxidase inhibitors.

Great caution should be exercised if mianserin is used in patients receiving barbiturates, anti-convulsant therapy or narcotic analgesics. Adjustment of dosage will likely be required.

Additional monitoring procedures are recommended for patients receiving concurrent anticoagulant therapy of the

coumarin type (e.g. warfarin).

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

4.6 Fertility, pregnancy and lactation

Mianserin is not recommended for use during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

The most commonly occurring side effect is drowsiness, particularly during the first few days of treatment. Patients should be warned of the possible hazard in driving or operating machinery. Any drowsiness may be potentiated by alcohol.

4.8 Undesirable effects

As an improvement may not occur during the first 2-4 weeks of treatment patients should be closely monitored during this period.

It is advisable to maintain treatment with mianserin for several months after initial clinical improvement.

In order to ensure an optimal antidepressant effect the dosage of mianserin should not be reduced.

The frequency and severity of depression-related symptoms such as blurred vision, dry mouth and constipation do not usually increase during treatment with mianserin; in fact an actual decrease has been observed in many cases.

Cases of suicidal ideation and suicidal behaviours have been reported during mianserin therapy or early after treatment discontinuation (see section 4.4).

Bone marrow depression, usually presenting a granulocytopenia or agranulocytosis, has been reported during treatment with mianserin. These reactions have occurred most commonly after 4-6 weeks and were generally reversible on stopping treatment. A full blood count is recommended every four weeks during the first three months of treatment. In addition, monitoring of the patient's clinical condition should continue and if a patient develops fever, sore throat, stomatitis or other signs of infection, treatment should be stopped and a full blood count obtained. These adverse reactions have been observed in all age groups but appear to be more common in the elderly.

Jaundice, usually mild, hypomania and convulsions have also been reported at therapeutic dosage and under such circumstances treatment should be withdrawn.

The most commonly occurring side effect is drowsiness. Additional adverse effects that may occur include breast disorders (gynaecomastia, nipple tenderness and non-puerperal lactation), disturbances of liver function, arthralgia, dizziness, postural hypotension, oedema, polyarthropathy, skin rash, sweating and tremor.

Akathisia and hyperglycaemia have been reported following treatment with Mianserin.

Psychotic manifestations, including mania and paranoid delusions, may be exacerbated during antidepressant therapy.

The following adverse effects although not reported with mianserin can occur with tricyclics and bridged tricyclics: interference with sexual function in adults; withdrawal symptoms, (e.g. neuro-muscular irritability in neonates whose mothers received tricyclic or bridged tricyclic antidepressants during pregnancy).

4.9 Overdose

Symptoms of overdosage are normally confined to prolonged sedation. Cardiac arrhythmics, concussions, severe hypotension and respiratory depression are unlikely to occur. There is no specific antidote. Treatment is by gastric lavage with appropriate symptomatic and supportive therapy for usual functions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mianserin is a tetracyclic antidepressant. It does not appear to have significant anti-cholinergic properties, but has a marked sedative action. Unlike amitriptyline, it does not prevent the peripheral re-uptake of noradrenaline; it blocks presynaptic alpha-adrenoceptors and increases the turnover of brain noradrenaline. It has little effect on central serotonin uptake but has been shown to increase peripheral serotonin uptake in depressed subjects. It has antihistamine properties. Although many of the effects of mianserin differ from those of amitriptyline, its activity in depression is similar. Like amitriptyline, its mode of action in depression is not fully understood.

5.2 Pharmacokinetic properties

Mianserin is readily absorbed from the gastro-intestinal tract, but its bioavailability is reduced to about 70% by extensive first-pass metabolism in the liver.

Paths of metabolism of mianserin include aromatic hydroxylation, N-oxidation and N-demethylation.

Mianserin is excreted in the urine, almost entirely as its metabolites, either free or in conjugated form; some is also found in the faeces.

Mianserin is widely distributed throughout the body and is extensively bound to plasma proteins. It has been found to have a biphasic plasma half-life with the duration of the terminal phase ranging from 6 to 29 hours. Although plasma concentrations of mianserin vary widely between individuals there are some indications of a correlation with therapeutic response.

Mianserin crosses the blood-brain barrier. Studies, *in-vitro* and in animals have suggested that only small amounts cross the placenta and are excreted in breast milk.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>The tablet contains:</u>
Pregelatinised maize starch
Colloidal anhydrous silica
Microcrystalline cellulose
Anhydrous dibasic calcium phosphate
Magnesium stearate

<u>The film coat contains:</u>
Talc
Opadry white 03B28796 consisting of:
Hypromellose (E464)

Titanium dioxide (E171)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

1 year

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polypropylene tablet containers with polyethylene caps and PVC/foil blister packs of 100, 250 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
12 Station Close
Potters Bar
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 405/22/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th September 1988

Date of last renewal: 23rd May 2007

10 DATE OF REVISION OF THE TEXT

April 2011