SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mianserin 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mianserin Hydrochloride BP 10 mg per tablet

Excipients: Lactose monohydrate

Each tablet contains 73.7 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Biconvex film-coated tablets for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptoms of depressive illness.

4.2 Posology and method of administration

The tablets should be swallowed whole without chewing.

The daily dose can be taken either in divided doses or as a single dose at night (due to the favourable effect on sleep).

It is often advantageous to maintain antidepressant treatment for several months after clinical improvement has occurred.
**Adults**
Initially 30 – 40 mg daily in divided doses or as a single dose at bedtime, increased gradually as necessary. The usual dose range is 30 – 90 mg. Divided doses of up to 200 mg are well tolerated.

**Elderly**
The use of Mianserin is restricted to patients over 65 who:

1. Do not respond to other antidepressant drugs.
2. Have glaucoma.
3. Have prostatic hypertrophy.

Initial dose: not more than 30 mg daily. Any increase in dose should be under close medical supervision. A lower maintenance dose than usual may be sufficient to produce a clinical response (see section 5.2).

**Children**
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 precautions for use).

**Route of Administration**
Oral.

4.3 Contraindications
- Mania.
- Severe liver disease
- Hypersensitivity to mianserin or to any of the excipients.

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 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 anti-depressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient 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 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 drug therapy 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.

It may be 2 - 4 weeks from the start of treatment before there is an improvement in the patients depression; the patient should be closely monitored during this period.

Haematological and hepatic reactions
Mianserin has been associated with haematological and hepatic reactions and patients require careful supervision. A full blood count is recommended every 4 weeks during the first 3 months of treatment; subsequent clinical monitoring should continue and treatment should be stopped and a full blood count obtained if fever, sore throat, stomatitis or other signs of infection develop.

Cardiac effects
Care should always be taken in patients with recent myocardial infarction, arrhythmia or heart block. Serious cardio toxic effects appear to be rare at therapeutic dosage, even in patients with pre-existing cardiac disease, recent myocardial infarction or cardiac insufficiency.

Use in the Elderly
Elderly patients are less liable to experience adverse reactions such as agitation, confusion and postural hypotension, with mianserin than with tricyclics or bridged tricyclics, but all anti-depressant therapy should be used with caution in these patients.

Hypomania
There are indications that mianserin, like other anti-depressants, may precipitate hypomania in susceptible subjects with bipolar affective illness. In such a case treatment with mianserin should be withdrawn.

**Diabetes, hepatic or renal insufficiency**
Patients with diabetes, hepatic or renal insufficiency, normal precautions should be exercised and the dosages of any concurrent therapy kept under review. Patients with narrow angle glaucoma or prostatic hypertrophy should be monitored closely even though anticholinergic side-effects are not anticipated with mianserin therapy.

**Epilepsy**
As with tricyclic antidepressants mianserin is known to lower the convulsion threshold and should therefore be used with extreme caution in patients with epilepsy and other predisposing factors, e.g. brain damage of varying aetiology, concomitant use of neuroleptics, withdrawal from alcohol or drugs with anticonvulsive properties (e.g. benzodiazepines) (see section 4.5 and section 4.8).

**Surgery**
Prior to surgery the anaesthetist should be informed that the patient is being treated with mianserin.

**Phaeochromocytoma**
Care should always be taken in patients with phaeochromocytoma.

**Lactose**
With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose malabsorption should not take this medicine. The central nervous depressant action of alcohol may be potentiated by mianserin.

### 4.5 Interaction with other medicinal products and other forms of interaction

Mianserin should not be started until 2 weeks after stopping MAOIs; also MAOIs should not be started until at least 1-2 weeks after stopping tricyclic-related anti-depressants

Mobeclamide should not be started until at least 1 week after stopping mianserin administration.

There are no literature reports of interactions between sympathomimetic agents.

Phenytoin levels should be monitored in patients treated with mianserin because phenytoin can cause reduced plasma concentration.
Carbamazepine and phenobarbital accelerate the metabolism of mianserin and can cause reduced plasma concentration.

Mianserin may antagonise the anticonvulsant effect of antiepileptics, barbiturates and primidone by lowering the convulsive threshold. Caution is advised in patients with epilepsy and other predisposing factors such as brain damage, concomitant use of neuroleptics, withdrawal from alcohol.

There are no reports of interaction with the anti-hypertensives bethanidine, clonidine, guanethidine or propranolol, however monitoring of blood pressure should be carried out in patients concurrently treated with these drugs.

There may be an enhanced hypotensive effect if mianserin is taken with diazoxide, hydralazine or nitroprusside.

Alcohol, anxiolytics, hypnotics and antipsychotics have an enhanced sedative effect when taken with mianserin.

In patients taking anti-coagulant therapy of the coumarin type (e.g. warfarin), mianserin can be taken but additional close monitoring procedures should be undertaken.

Antihistamines and antimuscarinics may have increased antimuscarinic effects if taken with mianserin and antihistamines may have sedative effects.

Mianserin may reduce the effect of sublingual nitrates due to dry mouth.

Avoid the concomitant use of mianserin with apraclonidine, brimonidine, sibutramine, or artemether with lumefantrine.

There may be increased risk of convulsions when antidepressants given with atomoxetine.

4.6 **Fertility, Pregnancy and lactation**

Mianserin should not be used during pregnancy nor during breast feeding.

Do not use during pregnancy unless there are compelling reasons. There is no evidence of safety in human pregnancy. Animal studies have not shown hazard.

4.7 **Effects on ability to drive and use machines**
Patients should be warned of the possibility of drowsiness, particularly during the first few days of treatment and therefore the possible hazard of driving or operating machinery. Any drowsiness may be potentiated by alcohol.

4.8 Undesirable effects

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.

A small number of cases of bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, have been reported during treatment with mianserin; this is generally reversible upon stopping of 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. The reported cases of bone marrow depression are higher in the elderly.

Mild jaundice, hypomania and convulsions have been reported. If this occurs treatment should be stopped.

Additional adverse effects that may occur include breast disorders (gynaecomastia, nipple tenderness and non-puerperal lactation), disturbances of liver function, dizziness, postural hypotension, oedema, polyarthropathy, arthritis, arthralgia, skin rash, sweating and tremor. Leucopenia, agranulocytosis and aplastic anaemia (particularly in the elderly).

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; withdrawal symptoms in adults; withdrawal symptoms (e.g. neuro-muscular irritability) in neonates whose mothers received tricyclic or bridged tricyclic antidepressants during pregnancy.

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

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

Symptoms
Symptoms of overdose may include nausea and vomiting; dry mouth; constricted or dilated pupils; nystagmus; dizziness; ataxia; slow tendon reflexes; drowsiness; convulsions and coma. Cardiovascular effects reported include tachycardia or bradycardia; hypotension or hypertension; ECG abnormalities including ST elevation; PR interval shortening; first degree to complete heart block. In severe cases ventricular fibrillation and cardiac arrest may develop.

Features of serotonin toxicity may occur. These include CNS effects (including agitation or coma); autonomic instability (including hyperpyrexia); and neuromuscular excitability (including clonus and raised serum creatine kinase) This syndrome is more likely to occur if the patient has been exposed to two or more drugs that increase the effect of serotonin in serotonergic synapses (by increasing release, reducing reuptake or metabolism, or stimulating serotonin receptors), either as an acute overdose or if taken regularly, for example - SSRIs, MAOIs, tricyclic antidepressants, venlafaxine, tramadol, triptans, linezolid and St John's Wort, stimulant drugs of abuse (e.g. MDMA (ecstasy), amphetamines, cocaine, cathinone derivatives (mephedrone, etc).

The cardiovascular and CNS effects in overdose will be potentiated by simultaneous ingestion of alcohol, cardiovascular agents and other psychotropic drugs.

Management
Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.

The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) if the patient presents within 1 hour of ingestion of more than 5 mg/kg of bodyweight.

The patient should be observed for at least 6 hours after ingestion. Symptomatic patients should be observed for a minimum of 24 hours, due to the potential for delayed cardiac effects. U&Es and glucose levels should be checked.

A 12 lead ECG should be performed, and BP, pulse and cardiac rhythm should be monitored. Perform an arterial blood gases test in patients showing ECG abnormalities. Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Bradyarrhythmias and tachyarrhythmias should be treated appropriately.

If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered. Manage in a critical care area or involve the critical care outreach team. When hypotension is mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of vasopressor should be titrated against blood pressure. When hypotension is believed to be due to reduced cardiac output (e.g. where global hypokinesia is demonstrated on echocardiography) inotropic drugs such as dobutamine, or in severe cases adrenaline, may be beneficial.
NB. Both negative inotropic and vasodilator actions may both be present, particularly in mixed overdoses.

If severe hypotension further persists, discuss with your local poisons information service.

For symptomatic bradycardia give atropine intravenously, 0.5-1.2 mg for an adult or 0.02 mg/kg for a child. Repeat doses may be necessary. Dobutamine or isoprenaline may be considered if bradycardia is associated with hypotension. Temporary pacemaker insertion may be required; alternatively external pacing may be used.

Single brief convulsions do not require treatment.

Give oxygen, check blood glucose, U&Es and ABG. Correct acid base and metabolic disturbances as required.

If convulsions are frequent or prolonged, control with intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children) or lorazepam (4 mg in an adult and 0.1 mg/kg in a child).

If unresponsive to the above measures, consider phenobarbital sodium (10 mg/kg at maximum rate of 100 mg/minute; maximum dose 1 g). An alternative is phenytoin (loading dose 18 mg/kg IV infusion in adults and children, given via slow IV infusion [maximum rate 50 mg/minute] over 20-30 minutes with BP and ECG monitoring). However, the use of phenytoin may worsen cardio toxicity in the presence of sodium channel blocking agents.

If convulsions persist, consider the need for referral to intensive care, general anaesthesia, intubation and ventilation. There may continue to be epileptiform activity and measures to monitor and control this are necessary. Use of cerebral monitoring is therefore recommended. Thiopental is the preferred antiepileptic for status epilepticus not responding to the above measures. The role of newer agents such as propofol and levetiracetam in toxicological seizures is currently unclear because of a lack of clinical or animal studies.

Other measures should be taken as indicated by the patient's clinical condition.

Paediatrics
Children failing to respond to an appropriate intravenous fluid bolus require early discussion with the local paediatric intensive care unit (PICU).

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Antidepressants
ATC code: N06AX03
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 39 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.

Pharmacokinetic studies of mianserin in the elderly patient suggest a longer half-life and slower metabolic clearance. This information implies that a single night time dose of mianserin should be preferable to the divided dose in the elderly patient; in addition a lower than normal maintenance dose may be sufficient to produce a satisfactory clinical response.

5.3 **Preclinical safety data**

None available.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose BP  
Maize Starch BP  
Povidone BP  
Sodium Starch Glycollate BP  
Magnesium Stearate BP  
Colloidal Silicon Dioxide BP  
Isopropyl Alcohol BP

Film Coating Solution  
Opadry White Y-1-7000B E171, E132  
Purified Water BP

6.2 Incompatibilities

None reported.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a cool dry place and protect from light.

6.5 Nature and contents of container

Polypropylene tubular container with an open end equipped to accept a polyethylene closure, with a tamper-evident tear strip or PVdC coated PVC/Aluminium blisters (60gm/m² PVdC on 250µm PVC/20µm A1) in pack sizes of 28, 50, 100, 250 and 500 tablets.
6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1228

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

30 August 1988 / 18 September 1998

10 DATE OF REVISION OF THE TEXT

18/04/2012