SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bonserin®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Mianserin Hydrochloride 30mg per tablet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the treatment of depression.

4.2 Posology and method of administration
Posology
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. In order to ensure an optimal antidepressant effect the dosage of mianserin should not be reduced.

Adults
Treatment should usually commence with 30 mg mianserin per day increasing gradually as necessary. The effective dosage usually lies between 30 mg and 90 mg. Divided doses of up to 200 mg are well tolerated.

Older people
The use of mianserin is restricted to patients over 65 who:
- do not respond to other antidepressant drugs
- have glaucoma
- have prostatic hypertrophy

Not more than 30 mg a day initially. Any increase in dose should be under close medical supervision. A lower than normal maintenance dose may be sufficient to produce a satisfactory clinical response.

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 older people; in addition a lower than normal maintenance dose may be sufficient to produce a satisfactory clinical response.

Paediatric population
Mianserin should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Method of administration
For oral use.
The tablets should be swallowed without chewing.
If the tablet is halved in order to make the swallowing easier, both half tablets must be taken.

4.3 Contraindication
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Mania.
Severe liver disease.

4.4 Special warnings and precautions for use
Paediatric population
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) 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. 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.

As an improvement in the patient's depression may not occur during the first 2-4 weeks of treatment with mianserin, patients 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, heart block or arrhythmia.

Serious cardiotoxic effects appear to be rare at therapeutic dosage, even in patients with pre-existing cardiac disease, recent myocardial infarction or cardiac insufficiency.

Use in older people
Older people 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 this group of patients.

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

Diabetes, hepatic or liver impairment
When treating patients with diabetes, hepatic or renal insufficiency, normal precautions should be exercised and the dosages of any concurrent therapy kept under review.

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

Hypomaina
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.

Surgery
If surgery is necessary during mianserin therapy the anaesthetist should be informed of the treatment being given.

Phaeochromocytoma
Care should always be taken in patients with phaeochromocytoma.

Lactose
The tablets contain lactose. Each tablet contains 123 mg lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Mianserin may potentiate the central nervous depressant action of alcohol, anxiolytics, hypnotics and antipsychotics.

Mianserin should not be started within two weeks of cessation of therapy of Mono Amine Oxidase Inhibitors (MAOIs). MAOIs should not be started until at least 1 to 2 weeks after stopping tricyclic related antidepressants.

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

Phenytoin plasma levels should be monitored in patients treated concurrently with mianserin.

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 (see section 4.4). Caution is advised in patients with epilepsy and other predisposing factors such as brain damage, concomitant use of neuroleptics, withdrawal from alcohol.

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

Interactions with sympathomimetic agents have not been reported, and are unlikely.

Clinical experience has shown that mianserin does not interact with the antihypertensives bethanidine, clonidine, guanethidine or propranolol.
Nevertheless, the monitoring of blood pressure is recommended for those patients receiving concurrent anti-hypertensive therapy.

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

Concurrent anticoagulant therapy of the coumarin type (e.g.warfarin) is permissible, but close additional monitoring procedures should be carried out.

Antihistamines and antimuscarinics may have increased antimuscarinic effects if take 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breastfeeding
Mianserin is contraindicated during breast feeding. Breast feeding should be discontinued if treatment with mianserin is considered essential.

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
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.

Adverse events are listed below by system organ class and frequency. Frequencies are

defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) very rare (<1/10,000) and not known (cannot be estimated from available data).

Blood and lymphatic disorders
Not known: Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis has been reported during treatment with mianserin[1]. Leucopenia and aplastic anaemia.

Metabolism and nutrition disorders
Not known: Hyponatraemia[2]

Psychiatric disorders
Not known: Suicidal ideation, suicidal behaviour[3]. Psychotic manifestations, including mania and paranoid delusions, may be exacerbated during antidepressant therapy. Interference with sexual function in adults[4], withdrawal symptoms in adults[4], withdrawal symptoms (e.g. neuro-muscular irritability) in neonates whose mothers received tricyclic or bridged tricyclic antidepressants during pregnancy[4]. Hypomania has also been reported at therapeutic dosage and under such circumstances treatment should be withdrawn.

Nervous system disorders
Not known: Dizziness, drowsiness, tremor. Convulsions have also been reported at therapeutic dosage and under such circumstances treatment should be withdrawn.

Vascular disorders
Not known: Postural hypotension

Hepatobiliary disorders
Not known: Disturbances of liver function. Jaundice, usually mild, has also been reported at therapeutic dosage and under such circumstances treatment should be withdrawn.

Skin and subcutaneous tissue disorders
Not known: Skin rash, sweating

Musculoskeletal and connective tissue disorders
Not known: Arthralgia, polyarthropathy, arthritis

Reproductive system and breast disorders
Not known: Breast disorders (gynaecomastia, nipple tenderness and nonpuerperal lactation).

General disorders and administration site conditions
Not known: Oedema

[1]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 (see section 4.4). These adverse reactions have been observed in all age groups but appear to be more common in the elderly.

[2]Usually in the elderly, and possibly due to inappropriate secretion of antidiuretic hormone, hyponatraemia has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions whilst taking an antidepressant.

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

[4]Although not reported with mianserin, these adverse events can occur with tricyclics and bridged tricyclics

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose
Symptoms
Symptoms of overdosage 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.

Treatment
There is no specific antidote.

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 alphaadrenergic 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.

Paediatric population
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, other 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

Absorption
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.

Distribution
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.

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

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

5.3. Pre-clinical 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
Lactose, cellulose microcrystalline, pigment blend green, magnesium stearate, silicon dioxide colloidal.
Each tablet contains 123 mg lactose monohydrate.

6.2 Incompatibilities
None reported.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C in the original package.

6.5 Nature and contents of container
PVC/Aluminium blisters in pack size of 20 tablets.

6.6 Special precautions for disposal
None.

7. REGISTRATION HOLDER
Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.
Registration number: 043 28 26084.
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