

NEW ZEALAND DATA SHEET

Name of Medicine

Tolvon
Tablets
Mianserin hydrochloride 30 mg

Presentation

30 mg tablet: white, oval, biconvex, coded CT/7 on one side, ORGANON on the other side. Each film-coated tablet contains 30 mg of mianserin hydrochloride.

Uses

Actions

Mianserin, the active component of TOLVON, 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. TOLVON increases central noradrenergic neurotransmission by α_2 -autoreceptor blockade and noradrenaline-reuptake inhibition. In addition, interactions with serotonin receptors in the central nervous system have been found. Human pharmac-EEG studies have confirmed the antidepressant profile of TOLVON. The antidepressant efficacy of TOLVON 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 TOLVON is thought to be responsible for its sedative properties.

TOLVON is well tolerated, also by the elderly and by patients with cardiovascular disease. At therapeutically effective doses TOLVON 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. TOLVON does not antagonize the action of sympathicomimetic agents and antihypertensive medicines, which interact with adrenergic receptors (e.g. bethanidine) or α_2 -receptors (e.g. clonidine, methyldopa).

Pharmacokinetics

After oral administration of TOLVON the active constituent, mianserin is rapidly and well absorbed, reaching peak plasma levels within 3 hours. The bioavailability is approx. 20%. Binding of mianserin to plasma proteins is approx. 95%. The half-life of elimination (21-61 hours) is sufficient to justify once-a-day dosing. Steady-state plasma levels are reached within 6 days. Mianserin is extensively metabolized and eliminated via the urine and faeces within 7-9 days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation.

Indications

For relief of symptoms of depression in those cases of depressive illness where drug therapy is indicated.

Dosage And Administration

Adults

Dosage should be individually determined. Treatment should begin with 30 mg daily and dosage should be adjusted according to the clinical response. The effective dose usually lies between 30 and 90 mg (mostly 60 mg) daily.

Elderly

Dosage should be individually determined. Not more than 30 mg daily initially. The dose should be slowly increased under close supervision. A dose lower than is usual for adults may be sufficient for a satisfactory clinical response.

Children

TOLVON should not be used in patients under 18 years of age unless under the supervision of a specialist.

Administration

The tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

- The daily dose can be taken either in divided doses or preferably (in view of a favourable effect on sleep) as a single dose at night.
- Treatment with an adequate dose should result in a positive response within 2-4 weeks. In case of an insufficient response the dose can be increased. If there is no response within a further 2-4 weeks, then treatment should be stopped.
- It is recommended to maintain antidepressant treatment for 4-6 months after clinical improvement has occurred.
- Abrupt discontinuation of treatment with TOLVON very rarely causes withdrawal symptoms.

Contraindications

Mania.

Severe liver disease.

Hypersensitivity to mianserin or to any of the excipients.

Concomitant use of mianserin with monoamine oxidase (MAO) inhibitors (see **Interactions**). TOLVON is contraindicated for the treatment of depression in patients 12 years of age and under.

TOLVON is contraindicated for the treatment of nocturnal enuresis.

Warnings And Precautions

Use in Children and Adolescents Under 18 Years of Age

TOLVON 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 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.

Clinical Worsening and Suicide Risk

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or

not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until such improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients. The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, 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. Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adult and paediatric patients 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 the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that TOLVON is not approved for use in treating bipolar depression.

- Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with TOLVON. These reactions have occurred most commonly after 4-6 weeks of treatment and were generally reversible on stopping treatment; they have been observed in all age groups but appear to be more common in the elderly. If a patient shows fever, sore throat, stomatitis or other signs of infection, treatment should be stopped and a full blood count should be obtained.
- TOLVON, like other antidepressants, may precipitate hypomania in susceptible subjects with bipolar depressive illness. In such a case treatment with TOLVON should be discontinued.
- When treating patients with diabetes or cardiac disease, hepatic or renal insufficiency, normal precautions should be exercised and the dosages of any concomitant therapy kept under review.
- Patients with narrow angle glaucoma or symptoms suggestive of prostatic hypertrophy should also be monitored even though anticholinergic side effects are not anticipated with TOLVON therapy.
- Granulocytopenia, agranulocytosis and thrombocytopenia have been reported during treatment with TOLVON. Because most of the cases occurred in the first three months of treatment, the Medicines Adverse Reactions Committee has recommended

that there should be intensive clinical monitoring of the patient in the first three months with blood counts at a minimum of once per month. Patients should be warned to report symptoms or signs of sore throat, mouth ulcers, bowel upset or fever, to stop the medication immediately and to seek a consultation with the prescribing doctor.

- Treatment should be discontinued if jaundice occurs.
- Treatment should be discontinued if convulsions occur.

Information for Patients and Families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to this medicine's efficacy and safety when used in the treatment regimen proposed.

Use During Pregnancy And Breastfeeding

Although animal experiments indicate that TOLVON does not cause foetal harm and is excreted in the milk in very small amounts, the data in humans is limited and adverse effects have been seen with the use of other antidepressants. The benefits of the use of TOLVON during pregnancy or breast-feeding should be weighed against the possible hazards to the foetus or the newborn child.

Effects on Ability to Drive and Use Machines

TOLVON 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.

Adverse Effects

Depressive patients show a number of symptoms associated with the illness itself (dry mouth, obstipation, accommodation disturbances). Therefore, it is sometimes difficult to determine which symptoms are a consequence of the disease and which are a consequence of the treatment with TOLVON.

System organ class	Frequency estimate of undesirable effects		
	Common (> 1%)	Uncommon (0.1 – 1%)	Rare (< 0.1%)
Blood and the lymphatic system disorders			Blood dyscrasias, usually presenting as granulocytopenia or agranulocytosis (see also Warnings & Precautions)
Metabolism and nutrition disorders	Weight gain		
Psychiatric disorders			Hypomania
Nervous system disorders	Sedation occurring at initiating of treatment and decreasing as treatment continues (N.B. dose reduction generally does not lead to less sedation but can jeopardise		Convulsions Hyperkinesia (restless legs) Neuroleptic malignant syndrome (NMS)

System organ class	Frequency estimate of undesirable effects		
	Common (> 1%)	Uncommon (0.1 – 1%)	Rare (< 0.1%)
	antidepressant efficacy)		
Cardiac disorders			Bradycardia after the initial dose
Vascular disorders		Hypotension	
Hepato-biliary disorders	Elevated liver enzymes		Jaundice Hepatitis Hepatic function abnormal
Skin and subcutaneous tissue disorders		Exanthema	
Musculoskeletal, connective tissue and bone disorders		Arthralgia	
General disorders	Oedema		

Interactions

- TOLVON may potentiate the dampening action of alcohol on the central nervous system and patients should be advised to avoid taking alcohol during treatment.
- Mianserin should not be administered concomitantly with MAO inhibitors (such as moclobemide, tranylcypromine and linezolid) or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mianserin should be treated with MAO inhibitors (see Contraindications).
- TOLVON does not interact with bethanidine, clonidine, methyl dopa, guanethidine or propranolol (either alone or in combination with hydralazine). Nevertheless, it is recommended to monitor the blood pressure of those patients who are concomitantly treated with anti-hypertensive medicines.
- Concomitant treatment with antiepileptic drugs that are CYP 3A4 inducers (like phenytoin and carbamazepine), can result in reduced plasma levels of mianserin. Dose adjustment can be considered when concomitant treatment with these drugs is initiated or discontinued.
- As with other antidepressants TOLVON may affect the metabolism of coumarin derivatives like e.g. warfarin, necessitating supervision.

Overdosage

Symptoms of acute overdosage are generally confined to prolonged sedation. Cardiac arrhythmias, convulsions, severe hypotension and respiratory depression rarely occur. There is no specific antidote. Treatment is by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

Pharmaceutical Precautions

Store below 25°C.

Shelf-life 3 years.

List of Excipients

TOLVON 10, 20, 30 and 60 mg tablets contain:

Core: Potato starch, Silica colloidal anhydrous, Magnesium stearate, Methyl cellulose, Calcium hydrogen phosphate dihydrate.

Coating layer: Hypromellose, Macrogol 8000, Titanium dioxide (E171).

Medicine Classification

Prescription Medicine.

Package Quantities

TOLVON is available (in press-through safety strips) in 30 mg strength.
Packs - 30 x 30 mg tablets.

Further Information

Nil.

Name and Address

Merck Sharp & Dohme (NZ) Ltd
P O Box 99 851
Newmarket
Auckland 1149

Tel: 0800 500 673

Date of Preparation

20 January 2011

RA 1000 OS S4 (REF 3.0) April 2010