1. NAME OF THE MEDICINAL PRODUCT
Tolvon 10 mg tablets,
Tolvon 20 mg tablets,
Tolvon 30 mg tablets,
Tolvon 60 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10, 20, 30 or 60 mg of mianserin hydrochloride as active ingredient.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM
Tablet.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For relief of symptoms of depression in those cases of depressive illness where drug therapy is indicated.

4.2 Posology and method of administration
The tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

**Adults:** Dosage should be individually determined. An initial dose of 30 mg daily is recommended. The dose can be increased gradually every few days to obtain an optimal clinical response. The effective daily dose is usually between 60 and 90 mg.

**Elderly:** Dosage should be individually determined. The initial dose should be 30 mg daily. The dose can be increased gradually every few days. A lower dose than is usual for adults may be sufficient for a satisfactory clinical response.

**Children:** TOLVON should not be used in children and adolescents under the age of 18 years (see Section 4.4).

- 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.

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**
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.

**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 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, 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 antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behavior 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 therapy with antidepressants 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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

With regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of Tolvon tablets should be given to the patient.

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

4.5 Interaction with other medicinal products and other forms of interaction

- TOLVON may potentiate the dampening action of alcohol on the central nervous system and patients should be advised to avoid taking alcohol during treatment.
- TOLVON can be administered concomitantly with MAO inhibitors using the regular precautions with MAO inhibitors.
- TOLVON does not interact with bethanidine, clonidine, methyldopa, 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 antihypertensive drugs.
- As with other antidepressants TOLVON may affect the metabolism of coumarin derivatives like e.g. warfarin, necessitating supervision.

4.6 Pregnancy and lactation

Although animal experiments and limited human data indicate that mianserin does not cause foetal or neonatal harm and that mianserin is excreted in the mother milk in very small amounts only, the benefits of the use of TOLVON during pregnancy and breastfeeding should be weighed against the possible hazards to the foetus or the new-born child.

4.7 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.

4.8 Undesirable effects

Depressive patients show a number of symptoms associated with the illness itself (dry mouth, obsti-
pation, 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.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency estimate of undesirable effects</th>
<th>Common (&gt;1%)</th>
<th>Uncommon (0.1 - 1%)</th>
<th>Rare (&lt;0.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Blood dyscrasias, usually presenting as granulocytopenia or agranulocytosis (see also Section 4.4 «Special warnings and precautions for use»)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders*</td>
<td>Hypomania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>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 antidepressant efficacy)</td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td>Bradycardia after the initial dose</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td>Elevated liver enzymes</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Exanthema</td>
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<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Arthralgia</td>
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</tbody>
</table>

4.9 Overdose
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 is by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5. PHARMACOLOGICAL PROPERTIES
ATC code: N06A X03. Pharmacotherapeutic class: Antidepressants.

5.1 Pharmacodynamic properties
Mianserin, the active component of TOLVON, 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. TOLVON increases central noradrenergic neurotransmission by alpha2- autoreceptor blockade and noradrenaline-reuptake inhibition. In addition, interactions with serotonin receptors in the central nervous system have been found. Human pharmacoeEGG 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<sub>1</sub> and alpha1-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

* Cases of suicidal ideation and suicidal behaviors have been reported during mianserin therapy or early after treatment discontinuation (see section 4.4).
TCAs, it causes less cardiotoxic effects on overdose. TOLVON does not antagonize the action of sympathicomimetic agents and antihypertensive drugs, which interact with adrenergic receptors (e.g. bethanidine) or alpha2-receptors (e.g. clonidine, methyldopa).

5.2 Pharmacokinetic properties
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.

5.3 Preclinical safety data
No special particulars.

6. PHARMACEUTICAL PARTICULARS

6.1 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).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The shelf life for TOLVON tablets is 5 years.

6.4 Special precautions for storage
TOLVON should be stored in the dark and dry at 2-30°C.

6.5 Nature and contents of container
TOLVON tablets are round and biconvex (10 mg and 20 mg tablets) or oval, scored and biconvex (30 mg and 60 mg tablets). All tablets are marked with “Organon” on one side and a code on the other side.

Packaging 10 mg (code CT/4) and 20 mg (code CT/6) tablets:
Push-through strips of PVC-film and aluminium foil containing a heat-seal coating on the side in contact with the tablets.

Packaging 30 mg (code CT/7) and 60 mg (code CT/9) tablets:
Child-safe, push-through strips of opaque white PVC-film and aluminium foil containing a heat-seal coating on the side in contact with the tablets.

6.6 Instructions for use and disposal
Not applicable.

7. MARKETING AUTHORISATION HOLDER
N.V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands.

10. DATE OF REVISION OF THE TEXT
April 2008.