1. NAME OF THE MEDICINAL PRODUCT

Remeron 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of mirtazapine.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Oval, biconvex and marked with 'Organon' on one side-and a code TZ/5 on the other side .The tablets are red-brown and are scored.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Episode of major depression.

4.2 Posology and method of administration

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

Adults:

The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg (the higher dose should be taken at night).

Elderly:

The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children and adolescents under the age of 18 years:
In placebo- controlled trials, safety and efficacy of Remeron in the treatment of children and adolescents under the age of 18 years with major depressive disorder have not been established. Safety and efficacy in this population cannot be extrapolated from adult data. Therefore, Remeron should not be used in children and adolescents under the age of 18 years.

The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Remeron to this category of patients.

Mirtazapine has a half-life of 20-40 hours and therefore Remeron is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. Remeron may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued.Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

4.3 Contraindications

Hypersensitivity to mirtazapine or to any of the excipients.

4.4 Special warnings and special precautions for use

Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with Remeron. This mostly appears after 4-6 weeks of treatment and is in general reversible after termination of treatment. However, in very rare cases agranulocytosis has also been reported as a rare occurrence in clinical studies with Remeron. In postmarketing period with Remeron very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. All fatal cases concerned patients with an age above 65. The physician should be alert for symptoms like fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome; from clinical experience it appears that insults occur rarely in patients treated with Remeron
- hepatic or renal insufficiency
- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered
- low blood pressure.

Like with other antidepressants care should be taken in patients with:

- micturation disturbances like prostate hypertrophy (although problems are not to be expected because Remeron possesses only very weak anticholinergic activity)

- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Remeron because of its very weak anticholinergic activity)
- diabetes mellitus.

Treatment should be discontinued if jaundice occurs.

Moreover, like with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified
- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase

-with regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of Remeron tablets should be given to the patient

– although Remeron is not addictive, post- marketing experience shows that abrupt termination of treatment, treatment after long-term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizzines, agitation, anxiety, headache and nausea are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.

- elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with Remeron, side-effects have not been reported more often in elderly patients than in other age groups.

– from postmarketing experience it appears that serotonin syndrome occurs very rarely in patients treated with Remeron alone.

– interactions with other serotonergic drugs (see section 4.5).

<u>Serotonin syndrome</u>

Caution is advisable if Remeron is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan.

In rare cases, serotonin syndrome has been reported in patients using SSRIs or SNRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI/ SNRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in children, adolescents under 18 years of age and young adults ages 18-24

Remeron 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: 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 psychiatric disorders showed an increased risk of suicidality (suicidal ideation and suicidal behaviours) with antidepressants compared to placebo in patients less than 25 years old. The meta-analysis did not show an increas in the risk of suicidality with antidepressants compared to placebo in patients between the age of 25 and 65. There was a reduction with antidepressants compared to placebo in adults aged 65 and older.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

- Mirtazapine is extensively metabolized by CYP2D6 and CYP3A4, and to a lesser extent by CYP1A2. An interaction study of healthy volunteers showed that paroxetine, a CYP2D6 inhibitor, has no influence on mirtazapine pharmacokinetics at steady state. Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40% and 50% respectively.

Caution should be exercised when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin or nefazodone.

- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a 45 to 60% decrease in plasma mirtazapine concentrations. When carbamazepine or another inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.
- When cimetidine is co-administered, the bioavailability of mirtazapine may be increased by more than 50%. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is discontinued.
- In in vivo -interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine and phenytoin (CYP3A4 substrate), amitriptyline and cimetidine.
- No relevant clinical effects or changes in pharmacokinetics have been observed in humans on concurrent treatment with mirtazapine and lithium.

Pharmacodynamic interactions

- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy.
- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives. Caution should be exercised when these medicinal products are prescribed together with mirtazapine.
- Mirtazapine may increase the CNS depressant effect of alcohol. Patients should therefore be advised to avoid alcoholic beverages.
- If other serotonergic drugs (e.g. SSRI and venlafaxine) are used concomitantly with mirtazapine, there is a risk of interaction that could lead to the development of a serotonin syndrome.
- From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with mirtazapine in combination with SSRIs or venlafaxine. If the combination is considered therapeutically necessary, dosage changes should be made with caution and sufficiently close monitoring for signs of beginning serotonergic overstimulation maintained.
- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the INR in subjects treated with warfarin. As at a higher dose of mirtazapine a more pronounced effect can not be

excluded. It is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

4.6 Pregnancy and lactation

Although studies in animals have not shown any teratogenic effects of toxicological significance, the safety of Remeron in human pregnancy has not been established. Remeron should be used during pregnancy only if it is clearly needed.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of Remeron in breast feeding mothers is not recommended since no human data in breast milk are available.

4.7 Effects on ability to drive and use machines

Remeron has minor to moderate influence on the ability to drive and use machines.Remeron may impair concentration and alertness. Patients treated with antidepressants should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery.

4.8 Undesirable effects

- Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Remeron.

System organ class	**Very common (≥1/10)**	**Common (>1/100 to <1/10)**	**Uncommon (>1/1,000 to ≤1/100)**	**Rare (>1/10,000 to ≤1/1,000)**	**Very rare (≤1/10,000)**
Blood and the lymphatic system disorders				▪ Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anemia and thrombocytopenia) (see also section 4.4 'Special warnings and special precautions for use') ▪ Eosinophilia	
Metabolism and nutrition disorders		▪ Increase in appetite			
Psychiatric disorders				▪ Nightmares/vivid dreams ▪ Mania ▪ Agitation ▪ Confusion ▪ Hallucinations ▪ Anxiety *) ▪ Insomnia *) ▪ Psychomotor	

System organ class	Very common (≥1/10)	Common (>1/100 to <1/10)	Uncommon (>1/1,000 to ≤1/100)	Rare (>1/10,000 to ≤1/1,000)	Very rare (≤1/10,000)
				restlessness **)	
Nervous system disorders		▪ Somnolence (which can lead to impaired concentration), generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardize antidepressant efficacy). ▪ Dizziness ▪ Headache		▪ Convulsions (insults), tremor, myoclonus ▪ Paraesthesia ▪ Restless legs ▪ Syncope	▪ Oral paraesthesia
Vascular disorders				▪ (Orthostatic) hypotension	
Gastrointestinal disorders			▪ Nausea	▪ Dry mouth ▪ Diarrhea	▪ Oral hypoaesthesia ▪ Mouth oedema
Hepato-biliary disorders				▪ Elevations in serum transaminase activities	
Skin and subcutaneous tissue disorders				▪ Exanthema	
Musculoskeletal, connective tissue and bone disorders				▪ Arthralgia/myalgia	
General disorders and administration site conditions		▪ Generalised or local oedema		▪ Fatigue	
Investigations		▪ Weight gain			

*) Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under Remeron treatment, development or aggravation of anxiety and insomnia has been reported very rarely.
**) Incl. akathisia, hyperkinesia

4.9 Overdose

Present experience concerning overdose with Remeron alone indicates that symtoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension.
However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdosages.
Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions.
Activated charcoal or gastric lavage should also be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant
ATC code: NO6AX11

Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.

The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 Pharmacokinetic properties

After oral administration of Remeron, the active substance mirtazapine is rapidly and well absorbed (bioavailability $\approx$ 50%), reaching peak plasma levels after approx.2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

Mirtazapine is extensively metabolized and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. *In vitro* data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.
The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3 Preclinical safety data

Mirtazapine induced no effects of clinical relevance in chronic safety studies in rats and dogs or in reproductive toxicity studies in rats and rabbits. Mirtazapine was not genotoxic in a series of tests for gene mutation and chromosomal and DNA damage. Thyroid gland tumours found in a rat carcinogenicity study and

hepatocellular neoplasm found in a mouse carcinogenicity study are considered to be species-specific, non-genotoxic reponses associated with long-term treatment with high doses of hepatic enzyme inducers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Remeron 15 mg, 30 mg and 45 mg tablets contain:

Core: maize starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose

Coating layer: hypromellose, polyethylene glycol 8000, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Remeron should be stored at 2-30°C, dry and in the original package in order to protect from light.

6.5 Nature and contents of containers

child-safe, push-through strips made of opaque white polyvinyl chloride film and aluminium foil containing a heat-seal coating on the side in contact with the tablets.

The following packages are available:
Push- through strips with 10 tablets each. Packs containing 30 (3X10) tablets.

6.6 Instructions for use/handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Pharmagon Ltd., 10 Bareket street, POB 8154, Petach Tikva 49181.

8. MARKETING AUTHORIZATION NUMBER

108-28-28503-00

This leaflet format was set by MoH and its content has been reviewed and approved