Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mirap DisTab 30 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 30 mg of mirtazapine.

Excipients with known effect
Each orodispersible tablet contains 6 mg of aspartame (E951), 30 nanograms of sulphites and 0.093 mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.
White to off-white, round, flat tablets with bevelled edges and plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mirap DisTab is indicated in adults for the treatment of episodes of major depression.

4.2 Posology and method of administration

Posology

Adults
The effective daily dose is usually between 15 and 45 mg; the starting dose is 15 or 30 mg.
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.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

It is recommended to discontinue treatment with mirtazapine gradually to avoid withdrawal symptoms (see section 4.4).

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.

Renal impairment
The clearance of mirtazapine may be decreased in patients with moderate to severe renal impairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing Mirap DisTab to this category of patients (see section 4.4).

Hepatic impairment
The clearance of mirtazapine may be decreased in patients with hepatic impairment. This should be taken into account when prescribing Mirap DisTab to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

Paediatric population
Mirap DisTab should not be used in children and adolescents under the age of 18 years as efficacy was not demonstrated in two short-term clinical trials (see section 5.1) and because of safety concerns (see sections 4.4, 4.8 and 5.1).

Method of administration
Mirap DisTab has an elimination half-life of 20-40 hours and thereforeMirap DisTab is suitable for once daily administration. It should be taken preferably as a single night-time dose before going to bed. Mirap DisTab may also be given in two divided doses (once in the morning and once at night-time, the higher dose should be taken at night).
The tablets should be taken orally. The tablet will rapidly disintegrate and can be swallowed without water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Paediatric population
Mirap DisTab 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.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme, which can be life-threatening or fatal, have been reported in association with Mirap DisTab treatment.
If signs and symptoms suggestive of these reactions appear, Mirap DisTab should be withdrawn immediately.
If the patient has developed one of these reactions with the use of Mirap DisTab, treatment with Mirap DisTab must not be restarted in this patient at any time.

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 antidepressants 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 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 behaviour or thoughts and unusual changes in behaviour 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 the smallest amount of Mirap DisTab orodispersible tablets should be given to the patient consistent with good patient management, in order to reduce the risk of overdose.

Bone marrow depression
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been
reported during treatment with mirtazapine. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with mirtazapine. In the postmarketing period with mirtazapine very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases mostly 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.

Jaundice
Treatment should be discontinued if jaundice occurs.

Conditions which need supervision
Careful dosing as well as regular and close monitoring is necessary in patients with:
– epilepsy and organic brain syndrome: Although clinical experience indicates that epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Mirap DisTab should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency
– hepatic impairment: Following a single 15 mg oral dose of mirtazapine, the clearance of mirtazapine was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine was about 55 % increased.
– renal impairment: Following a single 15 mg oral dose of mirtazapine, in patients with moderate (creatinine clearance < 40 ml/min) and severe (creatinine clearance ≤ 10 ml/min) renal impairment the clearance of mirtazapine was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 %increased respectively. No significant differences were found in patients with mild renal impairment (creatinine clearance < 80 ml/min) as compared to the control group.
– cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarction, where normal precautions should be taken and concomitant medicinal products carefully administered.
– low blood pressure.
– diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dose may need to be adjusted and close monitoring is recommended.

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 bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania/hypomania should be closely monitored. Mirtazapine should be discontinued in any patient entering a manic phase.
– Although Mirap DisTab is not addictive, post-marketing experience shows that abrupt termination of 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, dizziness, 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 the underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.
– Care should be taken in patients with micturition disturbances like prostate hypertrophy and in patients with acute narrow-angle glaucoma and increased intra-ocular pressure (although there is little chance of problems with Mirap DisTab because of its very weak anticholinergic activity).
– Akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.
- Cases of QT prolongation, Torsade de Pointes, ventricular tachycardia, and sudden death, have been reported during the post-marketing use of mirtazapine. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc prolonging medicinal products (see section 4.5 and section 4.9). Caution should be exercised when Mirap DisTab is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval.

Hyponatraemia
Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported very rarely with the use of mirtazapine. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medicinal products known to cause hyponatraemia.

Serotonin syndrome
Interaction with serotonergic active substances: serotonin syndrome may occur when selective serotonin reuptake inhibitors (SSRIs) are used concomitantly with other serotonergic active substances (see section 4.5). Symptoms of serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma. Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine. Treatment with mirtazapine should be discontinued if such events occur and supportive symptomatic treatment initiated. From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with Mirap DisTab alone (see section 4.8).

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

Mirap DisTabcontains aspartame, benzyl alcohol, sulphites and sodium
This medicinal product contains 6 mg aspartame in each orodispersible tablet. Aspartame is a source of phenylalanine. It may be harmful for patients with phenylketonuria.
This medicinal product contains 0.093 mg of benzyl alcohol in each orodispersible tablet. Benzyl alcohol may cause allergic reactions. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment or during pregnancy or lactation because of the risk of accumulation and toxicity (metabolic acidosis). Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.

This medicinal product contains as ingredient of the peppermint flavour a very small amount of sulphites. These may rarely cause severe hypersensitivity reactions and bronchospasm.
This medicinal product contains less than 1 mmol (23 mg) sodium in each orodispersible tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
- Mirtazapine should not be administered concomitantly with MAO inhibitors or within two weeks after discontinuation of MAO inhibitor therapy. In the opposite way about two weeks should pass before patients treated with mirtazapine should be treated with MAO inhibitors (see section 4.3).
In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, methylene blue, SSRIs, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) may lead to an incidence of serotonin associated effects (serotonin syndrome: see section 4.4). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine.
- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, antihistamine H1 antagonists, opioids). 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 while taking mirtazapine.
- Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalized ratio (INR) in subjects treated with warfarin. As at a higher dose of mirtazapine a more pronounced effect cannot be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.
- The risk of QT prolongation and/or ventricular arrhythmias (e.g. Torsade de Pointes) may be increased with concomitant use of medicinal products which prolong the QTc interval (e.g. some antipsychotics and antibiotics).

Pharmacokinetic interactions
- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other 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.
- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40 % and 50 % respectively.
- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapine may increase more than 50 %.
Caution should be exercised and the dose may have to be decreased when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.
- Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptyline, risperidone or lithium.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited data of the use of mirtazapine in pregnant women do not indicate an increased risk for congenital malformations. Studies in animals have not shown any teratogenic effects of clinical relevance, however developmental toxicity has been observed (see section 5.3).
Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to mirtazapine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations).

Caution should be exercised when prescribing to pregnant women. If Mirap DisTab is used until, or shortly before birth, postnatal monitoring of the newborn is recommended to account for possible discontinuation effects.

Breast-feeding
Animal studies and limited human data have shown excretion of mirtazapine in breast milk only in very small amounts. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Mirap DisTab should be made taking into account the benefit of breast-feeding to the child and the benefit of Mirap DisTab therapy to the woman.

Fertility
Non-clinical reproductive toxicity studies in animals did not show any effect on fertility.

4.7 Effects on ability to drive and use machines

Mirap DisTab has minor or moderate influence on the ability to drive and use machines. Mirap DisTab may impair concentration and alertness (particularly in the initial phase of treatment). Patients should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery, at any time when affected.

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 Mirap DisTab.
The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with mirtazapine in randomized placebo-controlled trials (see below) are somnolence, sedation, dry mouth, weight increased, increase in appetite, dizziness and fatigue.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme have been reported in association with Mirap DisTab treatment (see section 4.4).

All randomized placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of mirtazapine. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1,501 patients (134 person years) receiving doses of mirtazapine up to 60 mg and 850 patients (79 person years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment. Table 1 shows the categorized incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with mirtazapine than with placebo, added with adverse reactions from spontaneous reporting. The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

Table 1. Adverse reactions of Mirap DisTab

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)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia thrombocytopenia),

					Eosinophilia
Endocrine disorders					Inappropriate antidiuretic hormone secretion,hyperprolactinemia (and related symptoms galactorrhea and gynecomastia)
Metabolism and nutrition disorders	Increase in appetite[1], weight increased[1]				Hyponatraemia
Psychiatric disorders		Abnormal dreams, confusion, anxiety[2, 5], insomnia[3, 5]	Nightmares[2], mania, agitation[2], hallucinations, psychomotor restlessness (incl. akathisia, hyperkinesia)	Aggression	Suicidal ideation[6], suicidal behaviour[6] , somnambulism
Nervous system disorders	Somnolence[1, 4], sedation[1, 4], headache[2],	Lethargy[1], dizziness, tremor, amnesia[7]	Paraesthesia[2], restless legs, syncope	Myoclonus	Convulsions (insults), serotonin syndrome, oral paraesthesia, dysarthria
Vascular disorders		Orthostatic hypotension	Hypotension[2]		
Gastro-intestinal disorders	Dry mouth	Nausea[3], diarrhea[2], vomiting[2], constipation[1]	Oral hypoaesthesia	Pancreatitis	Mouth oedema, increased salivation
Hepatobiliary disorders				Elevations in serum transaminase activities	
Skin and subcutaneous tissue disorders		Exanthema[2]			Stevens-Johnson-Syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculo-skeletal and connective tissue disorders		Arthralgia, myalgia, back pain[1]			Rhabdomyolysis
Renal and urinary disorders					Urinary retention
Reproductive System and breast disorder					Priapism
General disorders and administration site conditions		Oedema peripheral[1], fatigue			Generalised oedema, localised oedema
Investigations					Increased creatinine kinase

[1] In clinical trials this event occurred statistically significantly more frequently during treatment with mirtazapine than with placebo.
[2] In clinical trials these events occurred more frequently during treatment with placebo than with mirtazapine, however not statistically significantly more frequently.
[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with mirtazapine.
[4] N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy.
[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.
[6] Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see section 4.4).
[7] In most cases patients recovered after drug withdrawal.

In laboratory evaluations in clinical trials transient increases in transaminases and gamma-glutamyltransferase have been observed (however associated adverse events have not been reported statistically significantly more frequently with mirtazapine than with placebo).

Paediatric population:
The following adverse events were observed commonly in clinical trials in children: weight gain, urticaria and hypertriglyceridaemia (see also section 5.1).

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Present experience concerning overdose with mirtazapine alone indicates that symptoms 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 doses much higher than the therapeutic dose, especially with mixed overdoses. In these cases QT prolongation and Torsade de Pointes have also been reported.

Cases of overdose should receive appropriate symptomatic and supportive therapy for vital functions. ECG monitoring should be undertaken. Activated charcoal or gastric lavage should also be considered.

Paediatric population
The appropriate actions as described for adults should be taken in case of an overdose in paediatrics.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antidepressants, ATC code: NO6AX11

Mechanism of action/pharmacodynamic effects:
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.

Clinical efficacy and safety
The histamine H1-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has only limited effects (e.g. orthostatic hypotension) on the cardiovascular system.

The effect of mirtazapine on QTc interval was assessed in a randomized, placebo and

moxifloxacin controlled clinical trial involving 54 healthy volunteers using a regular dose of 45 mg and a supra-therapeutic dose of 75 mg. Linear e-max modelling suggested that prolongation of QTc intervals remained below the threshold for clinically meaningful prolongation (see section 4.4).
Paediatric population:
Two randomised, double-blind, placebo-controlled trials in children aged between 7 and 18 years with major depressive disorder (n=259) using a flexible dose for the first 4 weeks (15-45mg mirtazapine) followed by a fixed dose (15, 30 or 45 mg mirtazapine) for another 4 weeks failed to demonstrate significant differences between mirtazapine and placebo on the primary and all secondary endpoints. Significant weight gain (≥7%) was observed in 48.8% of the mirtazapine treated subjects compared to 5.7% in the placebo arm. Urticaria (11.8% vs. 6.8%) and hypertriglyceridaemia (2.9% vs. 0%) were also commonly observed.

5.2 Pharmacokinetic properties

Absorption:
After oral administration of Mirap DisTab, the active substance mirtazapine is rapidly and well absorbed (bioavailability ≈ 50 %), reaching peak plasma levels after approx. two hours. Food intake has no influence on the pharmacokinetics of mirtazapine.
Distribution:
Binding of mirtazapine to plasma proteins is approx. 85 %.
Biotransformation:
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.
Elimination
Mirtazapine is extensively metabolized and eliminated via the urine and faeces within a few days. 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.
Linearity/non-linearity
Mirtazapine displays linear pharmacokinetics within the recommended dose range.
Special populations:
The clearance of mirtazapine may be decreased as a result of renal or hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.
In reproductive toxicity studies in rats and rabbits no teratogenic effects were observed. At two-fold systemic exposure compared to maximum human therapeutic exposure, there was an increase in post-implantation loss, decrease in the pup birth weights, and reduction in pup survival during the first three days of lactation in rats.
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 neoplasms found in a mouse carcinogenicity study are considered to be species-specific, non-genotoxic responses associated with long-term treatment with high doses of hepatic enzyme inducers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Povidone K30
Crospovidone
Silica colloidal anhydrous
Aspartame (E951)
Calcium stearate
Orange flavour [maltodextrin, natural and artificial flavourings, dl-alpha-tocopherol, benzyl alcohol, sodium]

Peppermint flavour [maltodextrin, natural flavourings, dextrin, sulphites]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blisters containing 6, 18, 28, 30, 48, 84, 90 or 96 orodispersible tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/094/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date of first authorisation: 3rd August 2007.
Date of last renewal: 1st June 2010

10 DATE OF REVISION OF THE TEXT

September 2025