SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mirtazapine 30mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30mg of mirtazapine.

Excipient(s) with known effect
Each film-coated tablet contains 203.6 mg Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Brownish, scored on both sides, 12.7 x 6.5mm oval, biconvex, film-coated tablets. Marked with I on one side.

4.1 Therapeutic indications

Mirtazapine is indicated in adults for the treatment of major depressive episode.

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.
The antidepressive effect of mirtazapine usually becomes evident after 1 to 2 weeks use. Treatment with an adequate dose should result in a positive response within 2 to 4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. After having obtained an optimal clinical effect and the patient is free of symptoms, the treatment should be continued for 4 to 6 months, until a gradual discontinuation can be considered. If no clinical response is observed within 2 to 4 weeks of treatment with the maximum dose, the treatment should be gradually discontinued. Gradually tapering down the dosage is necessary to avoid withdrawal symptoms (see section 4.4).

Elderly patients: The recommended dose is the same as that for adults. In elderly patients, changes especially increments of dosage must be made cautiously and under close supervision to elicit a satisfactory and safe response.

Paediatric population
Mirtazapine should not be used in children and adolescents (under 18 years of age), as efficacy was not demonstrated in two short-term clinical trial (see section 5.1) and because of safety concern (see section 4.4, 4.8 and 5.1), the use is not recommended.

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 Mirtazapine 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 Mirtazapine to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

Method of administration
Mirtazapine tablets can be taken once daily, since the elimination half-life is 20 to 40 hours. The medicine should be taken preferably as a single dose immediately before bedtime. The daily dose can also be divided into two doses (taken in the morning and at the bedtime. The larger dose should be taken in the evening).
Take your tablets orally. The tablets should be swallowed whole without chewing, with a sufficient amount of fluid. The tablets can be taken with or without food.

4.3 Contraindications
Hypersensitivity to mirtazapine or 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

Mirtazapine 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 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 Mirtazapine tablets should be given to the patient consistent with good patient management, in order to reduce the risk of overdose.

<u>Bone marrow depression</u>

Bone marrow depression, which is usually manifested by granulocytopenia or agranulocytosis, has been reported in the users of mirtazapine. This effect is usually seen after 4 to 6 weeks of treatment, but it usually disappears after discontinuation of treatment. Reversible agranulocytosis has also 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 attendant doctor should be alert for fever, throat pain, stomatitis and other signs and symptoms suggestive of infection. If these manifestations occur, the treatment should be discontinued and a complete blood count should be taken.

Jaundice

The treatment should be discontinued in the presence of jaundice.

Conditions which need supervision

The medicinal product is to be used with caution, and careful monitoring to be applied in patients with:

- epilepsy or organic brain syndrome; although clinical experience indicates that epileptic seizures are rare during mirtazapine treatment, as with other antidepressants, Mirtazapine 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 impairement: 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.
- heart disease, such as conduction disturbances, angina pectoris or recent cardiac infarction, which requires conventional precautions and caution during concurrent administration of other medicinal products
- hypotension.
- diabetes mellitus: In patients with diabetes, antidepressants may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Like with other antidepressants, caution should be exercised when the medicinal product is administered to patients with:

- 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 Mirtazapine 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 realised 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 Mirtazapine 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, Torsades 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 medicines (see section 4.5 and section 4.9). Caution should be exercised when Mirtazapine 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.

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 mirtazapine treatment.

If signs and symptoms suggestive of these reactions appear, mirtazapine should be withdrawn immediately.

If the patient has developed one of these reactions with the use of mirtazapine, treatment with mirtazapine must not be restarted in this patient at any time.

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 medications 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 Mirtazapine alone (see section 4.8).

Elderly

Elderly 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.

Lactose

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interactions 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).

If other serotonergic drugs (e.g. SSRI, L-tryptophan, triptans, tramadol, linezolid, methylene blue, venlafaxine, lithium and St. John's Wort – Hypericum perforatum – preparations) are used concomitantly with mirtazapine, there is a risk of interaction that could lead to the development of a serotonin syndrome (see section 4.4). From postmarketing experience it appears that serotonin syndrome occurs very rarely in patients treated with mirtazapine alone or in combination with SSRIs. If the combination is considered therapeutically necessary, dosage changes should be made with caution and sufficiently close monitoring for signs of beginning serotonergic over stimulation maintained.

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. Torsades de Pointes) may be increased with concomitant use of medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics).

Pharmacokinetic interactions

Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40% and 50% respectively.

Carbamazepine and phenytoin CYP3A4 inducer, increased mirtazapine clearance about twofold, resulting in a decrease in average mirtazapine concentrations of 60% and 45%, respectively. 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 (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is co-administered, the bioavailability of mirtazapine may be increased by 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.

In *in vivo* -interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine (CYP3A4 substrate), amitriptyline and cimetidine.

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 effect or reproductive toxicity of clinical relevance, however developmental toxicity has been observed (see 5.3 Preclinical safety data).

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 Mirtazapine 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

Mirtazapine should be made taking into account the benefit of breastfeeding to the child and the benefit of Mirtazapine 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

Mirtazapine has minor or moderate influence on the ability to drive and use machines. Mirtazapine may impair concentration and alertness, especially in the beginning of treatment. This should be considered before engaging in tasks requiring special alertness and concentration, such as driving and operating dangerous machines.

4.8 Undesirable effects

Depressed patients display a number of signs and symptoms 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 mirtazapine treatment.

Summary of safety profile

The most commonly reported adverse reactions, occurring in more than 5 % of patients treated with Mirtazapine in randomised 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 mirtazapine treatment (see section 4.4).

Tabulated list of adverse reactions

All randomised 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 categorised 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 randomised placebo-controlled patient trials were observed with mirtazapine has been classified as ‘not known’.

Table 1. Adverse reactions of Mirtazapine

System organ class	Very common (≥1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10 000, <1/1000)	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 • Hyperprolactinem (and relat symptoms galactorrhea a gynecomastia)
Metabolism and nutrition disorders	• Weight increased[1] • Increase in appetite[1]				• Hyponatraemia
Psychiatric disorders		• Abnormal dreams • Confusion • Anxiety[2,5] • Insomnia[3, 5]	• Nightmares[2] • Mania • Agitation[2] • Hallucinations • Psycho motor restlessness (incl. akathisia, hyperkinesia)	• Aggression	• Suicidal ideation[6] • Suicidal behaviou • 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 syndror • Oral paraesthesia • Dysarthria
Vascular disorders		• Orthostatic hypotension	• Hypotension[2]		
Gastrointestinal disorders	• Dry mouth	• Nausea[3] • Diarrhea[2] • Vomiting[2] • Constipation[1]	• Oral hypoaesthesia	• Pancreatitis	• Mouth oedema • Increased salivati
Hepato-biliary disorders				• Elevations of hepatic transaminase levels	
Skin and subcutaneous tissue disorders		• Exanthema[2]			• Drug reaction wit eosinophilia and systemic sympton (DRESS) • Stevens-Johnson Syndrome • Dermatitis bullou • Erythema

					multiforme • Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		• Arthralgia • Myalgia • Back pain[1]			• Rhabdomyolysis
Renal and urinary disorders					• Urinary retention
Reproductive system and breast disorders					• Priapism
General Disorders and administration site conditions		• Oedema peripheral[1] • Fatigue			• Generalised Oedema • Localised oedema
Investigations					• Increased creatini kinase

[1]In clinical trials these events 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.

Paediatric population

The following adverse events were observed commonly in clinical trials in children: weight gain, urticaria and hypertriglyceridemia (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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 dosages much higher than therapeutic dose, especially with mixed overdoses. Overdoses is treated with activated charcoal, support of vital functions and symptomatic treatment. Gastric lavage may be considered, if necessary. In these cases QT prolongation and Torsades de Pointes have also been reported.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants

ATC code: N06AX11

Mechanism of action/pharmacodynamic effects

Mirtazapine is a presynaptic alpha2-antagonist, which increases noradrenergic and serotonergic neurotransmission in the central nervous system. The serotonergic effect is a result of a specific action on the 5-HT1-receptors, since mirtazapine blocks both the 5-HT2- and the 5-HT3-receptors. Both enantiomers of mirtazapine are active agents. The S (+) enantiomer blocks alpha2- and 5-HT2-receptors, whereas the R (-) enantiomer blocks 5-HT3-receptors.

Clinical efficacy and safety

The H1-antagonistic effect is considered to the cause of the sedative effect of mirtazapine. The anticholinergic effect of mirtazapine is minimal and within therapeutic doses there are seldom clinically significant cardiovascular adverse events (e.g. orthostatic hypotension).

The effect of Mirtazapine on QTc interval was assessed in a randomised, 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 (15-45 mg 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 mirtazapine tablets, the active substance mirtazapine is rapidly and well absorbed (bioavailability about 50%), reaching peak plasma levels after about 2 hours. Food intake has no influence on the pharmacokinetics of mirtazapine.

Distribution

About 85% of mirtazapine is bound to plasma proteins. Steady state concentrations are reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range.

Biotransformation

Biotransformation mainly occurs through demethylation and oxidation and subsequent conjugation. In vitro studies of human liver microsomes show that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the mirtazapine 8-hydroxy metabolite, whereas the CYP3A4 enzyme is assumed to be responsible for the formation of the N-demethyl and N-oxide metabolites. The demethyl metabolite is

pharmacologically active, and its pharmacokinetic profile is similar to that of non-metabolized drug.

Elimination

Mirtazapine is metabolized effectively and eliminated in urine and faeces over a few days.The mean half-life of elimination is 20 to 40 hours; longer half-lives, up to 65 hours, have occasionally been recorded but in young men the half-lives have been shorter. 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 patient populations

The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency.

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 reproductive 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.

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

Core:
Lactose monohydrate
Pregelatinised maize starch
Anhydrous colloidal silica
Croscarmellose sodium
Magnesium stearate.

Coating:
Hypromellose
Macrogol 8000
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blister package: Store in the original package. Keep the blister in the outer carton.
PP container: Store in the original package. Keep the container tightly closed.

6.5 Nature and contents of container

Pack sizes
28, 30, 60, 90 and 100 tablets in clear PVC/Al blister.
28, 30, 60, 90, 100 and 250 tablets in white/opaque polypropylene tablet containers and LDPE caps.

The pack sizes of more than 100 tablets are intended for hospital use. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Flamingo Pharma UK Ltd.
1st floor, Kirkland House,
11-15 Peterborough Road,
Harrow, Middlesex,
HA12AX, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 43461/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

08/02/2023