IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0281/134/001
Case No: 2083434

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pinewood Laboratories Ltd,

Ballymacarbry, **Clonmel**, **Co. Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Mirtaz, 30 Milligram

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/07/2010** until **12/07/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mirtaz 30mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 30 mg mirtazapine.

Excipient: aspartame 12.0 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

White or off-white, round, 10 mm in diameter, biconvex, uncoated tablet marked with M2.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Major depressive episode.

4.2 Posology and method of administration

For oral administration.
The tablet is placed with dry hands on the tongue where it is rapidly dissolved. Orodispersible tablets should be taken with water and with or without food.

Adults
The initial dose is preferably 15 mg or 30 mg, taken in the evening. The maintenance dose is usually between 15 mg and 45 mg per day.

Elderly patients
As in adults. Changes, especially increments of dosage must be made cautiously and under close supervision.

Children and adolescents (under 18 years of age)
Mirtazapine should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Renal or hepatic impairment
The elimination of mirtazapine may be slower in patients with renal or hepatic impairment. This must be considered when mirtazapine is prescribed for these patients.

Mirtazapine tablets can be taken once daily, since the half-life is 20 to 40 hours. The medicinal product 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 bedtime. The larger dose should be taken in the evening.

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.

4.3 Contraindications

Hypersensitivity to mirtazapine or to any of the excipients.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years old

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.

Bone marrow suppression, 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. However, in very rare cases agranulocytosis can be fatal. Reversible agranulocytosis has also been reported in rare cases in clinical trials on mirtazapine. In the post-marketing period with mirtazapine 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 attendant doctor should be alert for fever, throat, pain, stomatitis and other signs and symptoms suggestive of infection. If these manifestations occur, the treatment must be discontinued and a complete blood count must be taken.

The medicinal product is to be used with caution, and careful monitoring in patients with:
- epilepsy and 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. Antidepressants should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored.
- hepatic or renal failure
- 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.

Like with other antidepressants, caution should be exercised when this medicinal product is administered to patients with:
- micturition disturbances, such as prostatatic hyperplasia (although mirtazapine is only slightly anticholinergic)
- acute narrow-angle glaucoma and increased intra-ocular pressure (during mirtazapine treatment, the risk of these problems is very low because of the low anticholinergic effect of mirtazapine)
- gastro-intestinal obstruction or ileus (during mirtazapine treatment, the risk of these problems is very low because of the low anticholinergic effect of mirtazapine)
- 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.

Treatment should be discontinued in the presence of jaundice.

Like in the case of other antidepressants, the following should be considered:
- An exacerbation of psychotic symptoms may occur when patients with schizophrenia or other psychoses are treated with antidepressants; paranoid thoughts can also be intensified.
- When the depressive phase of a bipolar disorder is being treated, a switch to a manic phase may occur. In case of

manic reaction, treatment should be discontinued.

- **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 antidepressant drugs 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 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.
  With regard to the chance of suicide, in particular at the beginning of treatment, only a limited quantity of mirtazapine tablets should be given to the patient.
- Although antidepressants do not cause dependency, abrupt cessation of long-term treatment may cause anxiety, agitation, nausea, headache, and malaise.
- Elderly patients are often more sensitive, especially to the undesirable effects of antidepressants. In clinical studies of mirtazapine, the reported incidence of undesirable effects has not been any higher in elderly patients than in other age groups. However, the experience is still limited.
- Interactions of mirtazapine with other serotonergic medicinal products (e.g. SSRIs) are reported in section 4.5.

Serotonin syndrome (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, and autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occurs very rarely in patients treated with mirtazapine alone.

Mirtazapine tablets contain aspartame, which is a source of phenylalanine. It may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Mirtazapine should not be administered concomitantly with monoamine oxidase (MAO) inhibitors or within two weeks after discontinuation of MAO inhibitor therapy.

Mirtazapine may increase the sedating properties of benzodiazepines and other sedative active substances. Caution should be exercised when these medicinal products are prescribed together with mirtazapine as it may result in potentiation of their central nervous system-depressant adverse events.

Mirtazapine may increase the central nervous system depressant effect of alcohol and conversely. Patients should therefore be advised to avoid alcoholic beverages.

If other serotonergic medicinal products (e.g. SSRIs, SNRIs e.g. venlafaxine, TCAs and tramadol) 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 (SNRI). 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.

No relevant clinical effects or changes in pharmacokinetics have been observed in humans on concurrent treatment with mirtazapine and lithium.

Pharmacokinetic interactions
Mirtazapine is almost completely metabolized by cytochrome P_{450} (CYP) 2D6 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 area under the curve (AUC) of mirtazapine by approximately 40% and 50% respectively. Caution should be exercised when co-administering mirtazapine with potent CYP3A4 inhibitors, human immunodeficiency virus (HIV) protease inhibitors, azole antifungals, erythromycin ornefazodone.

Carbamazepine, a CYP3A4 inducer, 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 or phenytoin) 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 (CYP2D6 substrate) or paroxetine (CYP2D6 substrate and inhibitor), carbamazepine (CYP3A4 substrate and inducer), amitriptyline and cimetidine.

Mirtazapine dosed at 30 mg once daily caused a small but statistically significant increase in the international normalised ratio (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

There are no adequate data of the use of mirtazapine in pregnant women. Studies in animals have not shown any teratogenic effects or reproductive toxicity of clinical relevance (see 5.3). The potential risk for humans is unknown. Mirtazapine should not be used during pregnancy unless clearly indicated, following a careful clinical risk/benefit consideration.

It is unknown whether mirtazapine is excreted in human breast milk. Animal studies have shown excretion of mirtazapine in the 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 breast-feeding to the child and the benefit of mirtazapine therapy to the woman.

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 there is no evidence for the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with Mirtaz taking into account the related mechanisms of action (increase in serotonin concentrations).

4.7 Effects on ability to drive and use machines

Mirtazapine has a moderate influence on the ability to drive and use machines.
Mirtazapine may moderately 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. Drowsiness, a common adverse event, also represents a risk.

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.

The following frequency classification applies hereafter:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Rare: bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia, and thrombocytopenia) (see also 4.4), eosinophilia.

Nervous system disorders
Common: somnolence (which may impair alertness), usually occurring during the first few weeks of therapy (NB. dose reduction does not generally lead to less sedation but can jeopardize antidepressant efficacy); dizziness, and headache
Rare: syncope, convulsions (seizures), tremor, myoclonus, paraesthesias, and restless legs
Very rare: serotonin syndrome, oral paraesthesia

Gastrointestinal disorders
Uncommon: nausea
Rare: dry mouth and diarrhoea, vomiting
Very rare: oral hypoaesthesia, mouth oedema

Skin and subcutaneous tissue disorders
Rare: exanthema

Musculoskeletal, connective tissue and bone disorders
Rare: arthralgia and myalgia

Endocrine disorders
Rare: hyponatraemia
The majority of reports were associated with older patients.

Metabolism and nutrition disorders
Common: increased appetite and weight gain

Vascular disorders
Rare: (orthostatic) hypotension.

General disorders and administration site conditions
Common: generalised or local oedema and accompanying weight gain
Rare: fatigue
Although mirtazapine does not cause dependence, 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, nausea, anxiety and agitation are the most frequently reported . As advised in section 4.2, treatment with mirtazapine should be discontinued gradually.

Hepato-biliary disorders
Rare: elevations of hepatic transaminase levels

Psychiatric disorders
Rare: agitation, psychomotor restlessness (including akathisia, hyperakinesia), mania, confusion, hallucinations, anxiety*, insomnia*, and nightmares/vivid dreams

(*Anxiety and insomnia, which may be symptoms of depression, can develop and become aggravated. Under treatment with mirtazapine, development or aggravation of anxiety and insomnia has been reported very rarely.)

Frequency not known: Cases of suicidal ideation and suicidal behaviours have been reported during Mirtazapine

therapy or early after treatment discontinuation (see section 4.4).

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 the therapeutic dose, especially with mixed overdosages. Overdose is treated with activated charcoal, support of vital functions and symptomatic treatment. Gastric lavage may be considered, if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants
ATC code: NO6AX11

Mirtazapine is a presynaptic α_2 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-HT_1 receptors, since mirtazapine blocks both the 5-HT_2 and 5-HT_3 receptors. Both enantiomers of mirtazapine are active agents. The S(+) enantiomer blocks α_2 and 5-HT_2 receptors, whereas the R(-) enantiomer blocks 5-HT_3 receptors.
The H_1-antagonistic effect is considered to be the cause of the sedative effect of mirtazapine. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

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 to 4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range.

Metabolism and elimination
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.

Mirtazapine is metabolised effectively and eliminated in the urine and faeces over a few days. 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-metabolised drug substance.

Special patient populations
The clearance of mirtazapine may be decreased in patients with renal or hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity, genotoxicity, or reproductive toxicity.

Mirtazapine induced no effects of clinical relevance in chronic safety studies in rats or dogs and reproductive toxicity

studies in rats or rabbits. In reproductive toxicity studies in rats and rabbits at high dose levels, 20 and 17 times the maximum human dose on mg/m^2 basis, respectively, no teratogenic effects were observed. There was, however, an increase in post-implantation loss, a decrease in the pup birth weights, and a 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 deoxyribonucleic acid (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
Cellulose, microcrystalline
Heavy magnesium carbonate
Hydroxypropylcellulose
Crospovidone
Silica, colloidal anhydrous
L-Methionine
Cellulose, microcrystalline and Guar gum
Aspartame (E951)
Orange flavour
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Blister: Store in the original package in order to protect from moisture and light.
Tablet container: Store in the original tablet container and keep it tightly closed in order to protect from moisture and light.

6.5 Nature and contents of container

Al/Al blister:
Pack sizes: 6, 18, 30, 48, 90, 96, 180 (18 x 10 hospital pack) tablets.
Al/Al Peel-to-open, perforated unit dose blister:
Pack sizes: 6, 18, 30, 48, 90, 96, 180 (18 x 10 hospital pack) tablets.
Polypropylene or HDPE tablet container with a LDPE or LDPE/HDPE cap and desiccant:
Pack size: 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 281/134/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th July 2007

10 DATE OF REVISION OF THE TEXT

July 2010