IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0966/013/001
Case No: 2043671

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

Ergha Healthcare Ltd

Damastown, **Mulhuddart**, **Dublin 15**, **Ireland**

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

BexZis 30 mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of 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 **15/05/2008**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BexZis 30mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of mirtazapine.

Excipients

Each tablet contains 226.66 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Reddish brown, round tablets. One side of the tablet has a scoreline with the marking ”9” on one side of the scoreline and the number ”3” on the other. The other side of the tablet is marked with the number ”7207”. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of episodes of major depression.

4.2 Posology and method of administration

For oral administration.

The tablets should be swallowed whole without chewing, with a sufficient amount of fluid. The tablets can be taken 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): Since the safety and efficacy of mirtazapine have not been investigated in these patients, the use is not recommended. See section 4.4.

Renal or hepatic insufficiency: The elimination of mirtazapine may be slower in patients with renal or hepatic insufficiency. This must be considered when mirtazapine is prescribed for these patients or the clinical responses are interpreted.

Mirtazapine tablets can be taken once daily, since the elimination 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 the 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 the active substance or to any of the excipients.
Concomitant use of mirtazapine with monoamine oxidase (MAO) inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Use in 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. 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 a limited number of BexZis Film-coated Tablets should be given to the patient.

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 post-marketing 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, 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 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 medicines carefully administered.
- low blood pressure.
- 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, 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 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 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 mirtazapine because of its very weak anticholinergic activity).
- Akathisia/psychomotor restlessness: the use of antidepressants has 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.

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 agents known to cause hyponatraemia.

Serotonin syndrome

Interaction with serotonergic active substances: serotonin syndrome may occur when selective serotonin re-uptake 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. From post-marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with mirtazapine alone (see section 4.8).

Elderly patients

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.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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, 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, histamine H_1 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.

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about two-fold, 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.

4.6 Pregnancy and lactation

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). Caution should be exercised when prescribing to pregnant women. If mirtazapine is used until, or shortly before birth, post-natal monitoring of the newborn is recommended to account for possible discontinuation effects.

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 breast-feeding to the child and the benefit of mirtazapine therapy to the woman.

4.7 Effects on ability to drive and use machines

Mirtazapine has minor or moderate influence on the ability to drive and use machines. It 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 mirtazapine.

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.

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 1501 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 mirtazapine

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)	Frequency not known
Investigations	Weight increased[1]				
Blood and lymphatic system disorders					Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenia) Eosinophilia
Nervous system disorders	Somnolence[1,4] Sedation[1,4] Headache[2]	Lethargy[1] Dizziness Tremor	Paraesthesia[2] Restless legs Syncope	Myoclonus	Convulsions (insults) Serotonin syndrome Oral

					paraesthesesia
Gastrointestinal disoders	Dry mouth	Nausea[3] Diarrhoea[2] Vomiting[2]	Oral hypoaesthesia		Mouth oedema
Skin and subcutaneous tissue disorders		Exanthema[2]			
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Back pain[1]			
Metabolism and nutrition disorders	Increase in appetite[1]				Hyponatraemia
Vascular disorders		Orthostatic hypotension	Hypotension[3]		
General disorders and administration site conditions		Oedema peripheral[1] Fatigue			
Hepatobiliary disorders				Elevations in serum transaminase levels	
Psychiatric disorders		Abnormal dreams Confusion Anxiety[2,5] Insomnia[3,5]	Nightmares[2] Mania Agitation[2] Hallucinations Psychomotor restlessness (incl. akathisia, hyperkinesia)		Suicidal ideation[6] Suicidal behaviour[6]
Endocrine disorders					Inappropriate antidiuretic hormone secretion

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).

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

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 overdoses. 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: Other antidepressants

ATC code: N06AX11

Mirtazapine is a centrally-active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors.

The histamine H_1-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, the active substance mirtazapine is rapidly and well absorbed (bioavailability $\approx$ 50%), reaching peak plasma levels after approx. two 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 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 or genotoxicity.

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

Tablet core

Lactose monohydrate
Maize starch
Povidone K-30
Anhydrous colloidal silica
Magnesium stearate.

Coating

Hypromellose
Titanium dioxide (E 171)
Macrogol 400
Macrogol 6000
Yellow iron oxide (E 172)
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters: transparent or white opaque (*PVC/PVdC/Al*).

Pack sizes: 14, 20, 28, 30, 50, 60, 100 and 200 (2 x 100) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ergha Healthcare Ltd.
Damastown
Mulhuddart
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8 MARKETING AUTHORISATION NUMBER

PA 966/13/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2005

Date of last renewal: 15 May 2008

10 DATE OF REVISION OF THE TEXT

March 2010