

IRISH MEDICINES BOARD ACT 1995, as amended

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

PPA1473/025/003

Case No: 2083874

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

McDowell Pharmaceuticals

4 Altona Road, Lisburn, N. Ireland, BT27 5QB

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

Zispin SolTab 45mg, orodispersible tablet

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 **02/07/2010**.

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

Zispin SolTab 45mg, orodispersible tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 45mg of mirtazapine

Excipients: Aspartame (E951) and sucrose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible tablet

Product imported from the United Kingdom:

Round, white, standard bevelled-edge tablets marked with a code on one side TZ/3

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Episode of major depression.

4.2 Posology and method of administration

The tablet should be taken orally. The tablet will rapidly disintegrate and can be swallowed without water.

Adults:

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

Elderly:

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

Children and adolescents under the age of 18 years:

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

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

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

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose.

If there is no response within a further 2-4 weeks, then treatment should be stopped.

4.3 Contraindications

Hypersensitivity to Mirtazapine or to any of the excipients.

4.4 Special warnings and precautions for use

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

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

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

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

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Zispin possesses only very weak anticholinergic activity)
- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Zispin because of its very weak anticholinergic activity)
- diabetes mellitus.

Treatment should be discontinued if jaundice occurs.

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

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

- with regard to the chance of suicide, in particular at the beginning of treatment, only a limited amount of Zispin SolTab should be given to the patient

although antidepressants are 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 symptoms 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 underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with Mirtazapine gradually.

- elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with Zispin, undesirable effects have not been reported more often in elderly patients than in other age groups
- from post-marketing experience it appears that the serotonin syndrome occurs very rarely in patients treated with Zispin alone.
- Interaction with other serotonergic drugs (see section 4.5)

Zispin SolTab contains sugar spheres, containing sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine.

Zispin SolTab contains aspartame, a source of phenylalanine. Each tablet with 15 mg, 30 mg and 45 mg mirtazapine, corresponds to 2.6 mg, 5.2 mg and 7.8 mg phenylalanine, respectively. May be harmful for patients with phenylketonuria.

Use in children and adolescents under 18 years of age:

Zispin 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.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

- Mirtazapine is extensively metabolized by CYP2D6 and CYP3A4, and to a lesser extent by CYP1A2. An interaction study of healthy volunteers showed that paroxetine, a CYP2D6 inhibitor, has no influence on mirtazapine pharmacokinetics at steady state. Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40% and 50% respectively. Caution should be exercised when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin or nefazodone.
- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a 45 to 60% decrease in plasma mirtazapine concentrations. When carbamazepine or another inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.
- When cimetidine is co-administered, the bioavailability of mirtazapine may be increased by more than 50%. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is discontinued.

- In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of risperidone or paroxetine (CYP2D6 substrate), carbamazepine and phenytoin (CYP3A4 substrate), amitriptyline and cimetidine.
- No relevant clinical effects or changes in pharmacokinetics have been observed in humans on concurrent treatment with mirtazapine and lithium

Pharmacodynamic interactions

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

4.6 Pregnancy and lactation

Although studies in animals have revealed no evidence of teratogenic effects of toxicological significance, the safety of Zispin in human pregnancy has not been established. Zispin should be used during pregnancy only if it is clearly needed.

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

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 Zispin/mirtazapine taking into account the related mechanisms of action (increase in serotonin concentrations).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

System organ Class	Very common (≥ 1/10)	Common (> 1/100 to < 1/10)	Uncommon (> 1/1,000 to < 1/100)	Rare (> 1/10,000 to < 1/1,000)	Very rare (≤ 1/10,000)
Blood and the Lymphatic system disorders				• Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia and thrombocytopenia) (see also section 4.4 “Special warnings and special precautions for use”) • Eosinophilia	
Metabolism and nutrition disorders		• Increase in appetite			
Psychiatric disorders				• Nightmares/vivid dreams • Mania • Agitation • Confusion • Hallucinations • Anxiety * • Insomnia* •Psychomotor restlessness**	
Nervous system disorders		• Somnolence (which can lead to impaired concentration) generally occurring during the first few weeks of treatment (NB dose reduction generally does not lead to less sedation but can jeopardize antidepressant Efficacy) • Dizziness • Headache		• Convulsions (insults), tremor, myoclonus • Paraesthesia • Restless legs • Syncope	• Oral paraesthesia
Vascular disorders				• (Orthostatic) hypotension	

Gastrointestinal disorders			• Nausea	• Dry mouth • Diarrhoea	• Oral hypoaesthesia • Mouth oedema
Hepato-biliary disorders				• Elevations in serum transaminase activities	
Skin and subcutaneous tissue disorders				• Exanthema	
Musculoskeletal, Connective tissue and bone disorders				• Arthralgia/myalgia	
General disorders and administration site disorders		• Generalised or local oedema		• Fatigue	
Investigations		• Weight gain			

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

**) Incl. akathisia, hyperkinesia

4.9 Overdose

Present experience concerning overdose with Zispin alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation has been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdosages.

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

5 PHARMACOLOGICAL PROPERTIES

Zispin (mirtazapine) is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Zispin begins to exert its effect in general after 1-2 weeks of treatment.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant

ATC code: NO6AX11.

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-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 α_2 and 5-HT₂ receptors and the R(-) enantiomer by blocking 5-HT₃ receptors. The histamine H₁-antagonistic activity of mirtazapine is associated with its sedative properties. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 Pharmacokinetic properties

After oral administration of Zispin, the active constituent mirtazapine is rapidly and well absorbed (bioavailability $\approx$ 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men.

The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the pharmacokinetics of mirtazapine.

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

The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3 Preclinical safety data

Mirtazapine induced no effects of clinical relevance in chronic safety studies in rats and dogs or in reproductive toxicity studies in rats and rabbits. Mirtazapine was not genotoxic in a series of tests for gene mutation and chromosomal and DNA damage. Thyroid gland tumours found in a rat carcinogenicity study and hepatocellular neoplasm found in a mouse carcinogenicity study are considered to be species-specific, non-genotoxic responses associated with long-term treatment with high doses of hepatic enzyme inducers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar Spheres (sucrose and maize starch)
 Hypromellose (E464)
 Povidone K30
 Magnesium stearate
 Aminoalkyl methacrylate copolymer E
 Aspartame
 Citric acid Anhydrous
 Microcrystalline cellulose
 Mannitol (E421)
 Natural and Artificial orange colours (No. SN027512)
 Sodium Bicarbonate
 Crospovidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Child resistant, peel to open, rigid perforated blister, formed from a laminate of aluminium foil and plastic films sealed to a paper based laminate of aluminium foil coated with a heat seal laquer, in an overlabelled carton.

The plastic films contain: PVC (polyvinyl chloride), polyamide and polyester

-peel to open blisters each with 6 tablets

-packs containing 30 (5x6) tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

McDowell Pharmaceuticals

4 Altona Road

Lisburn BT27 5QB

Northern Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1473/25/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th April 2009

10 DATE OF REVISION OF THE TEXT

July 2010