Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zispin SolTab 15mg Orodispersible tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Zispin SolTab 15mg orodispersible tablet contains 15mg of mirtazapine.

Excipients:
Each Zispin SolTab 15mg orodispersible tablet contains 4.65 mg aspartame and 28 mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet
Product imported from the UK
Round, white tablets marked with a code on one side 'TZ/1'

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of episodes of major depression.

4.2 Posology and method of administration

Adults:

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

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:

Zispin should not be used in children and adolescents under the age of 18 years (see section 4.4)

Renal impairment

The clearance of mirtazapine may be decreased in patients with renal impairment (creatinine clearance <40 ml/min). This should be taken into account when prescribing Zispin 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 Zispin to this category of patients, particularly with severe hepatic impairment, as patients with severe hepatic impairment have not been investigated (see section 4.4).

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

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

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

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

4.3 Contraindications

Hypersensitivity to Mirtazapine 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

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 behavior 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 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 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 number of Zispin orodispersible 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 Zispin. 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. 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, Zispin 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 15mg oral dose of mitazapine, 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 15mg oral dose of mirtazapine, in patients with moderate (creatinine clearance < 40ml/min) and severe (creatinine clearance ≤ 10ml/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 < 80ml/min) as compared to the control group.

• 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.

▪ 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 care 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 Zispin 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 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.

- 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 Zispin because of it's very weak anticholinergic activity).

- Akathisia/ psychomotor restlessness: The use of antidepressant have been associated with the development of akathisia, characterised by 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 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, nyoclonus, 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 Zispin 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 Zispin , undesirable effects have not been reported more often in elderly patients than in other age groups.

Sucrose
Zispin 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.

Aspartame
Zispin 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 it may be harmful for patients with phenylketonuria.

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 subtances (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 antipsychotic, 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 can not 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 twofold, resulting in a decrease in plasma mirtazapine concentrations 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, azole antifungals, erythromycin, cimetidine or nefazodone.

· Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of mirtazapine with paroxetine, amitriptylin, risperidone or lithium.

4.6 Fertility, 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 Zispin is used until, or shortly before birth, postnatal, 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 Zispin should be made taking into account the benefit of breast-feeding to the child and the benefit of Zispin therapy to the woman.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in the 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 (inhibition of the re-uptake of serotonin).

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in the 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 (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 Zispin.

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

All ramdomized placebo-controlled trials in patients (including indications other than major depressive disorder) have been evaluated for adverse reaction of Zispin . The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1501patients (134 person years) receiving dosed of mirtazapine up to 60mg 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 Zispin 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 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 < 1/1,1000)**	**Frequency not known**
Blood and the lymphatic system disorders					▪Bone marrow depression (granulocytop-enia, agranulocyto-sis, aplastic anaemia and thrombocytop-enia) ▪Eosinophilia
Metabolism and nutrition disorders	▪Increase in appetite[1]				▪Hyponatraemia
Psychiatric disorders		▪Abnormal dreams ▪Confusion ▪Anxiety [2.5]	▪Nightmares ▪Mania ▪Agitation ▪Hallucinations ▪Psychomotor		▪Suicidal ideation[6] ▪Suicidal behaviour[6]

		▪Insomnia[3]	restlessnes ▪(incl. Akathisia, hyperkinesias)		
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 paraesthesia
Vascular disorders		▪Orthostatic ▪hypotension	▪Hypotension[2]		
Gastrointestinal disorders	▪Dry mouth	▪Nausea[3] ▪Diarrhea[2] ▪Vomiting[2]	▪Oral hypoaesthesia		▪Mouth Oedema
Hepato-biliary disorders				Elevations in serum transaminase activities	
Skin and subcutaneous tissue disorders		▪Exanthema[2]			
Musculoskeletal, connective tissue and bone disorders		▪Arthralgia ▪Myalgia ▪Back pain[1]			
General disorders and administration site disorders		▪Oedema peripheral[1] ▪Fatigue			
Investigations	▪Weight increased[1]				
Endocrine disorders					▪Inappropriate antidiuretics hormone secretion

1. In clinical trials these events occurred statistically significantly more frequent during treatment with Zispin than with placebo.

2. In clinical trials these events occurred more frequently during treatment with placebo than with Zispin, however not statistically more frequently.

3. In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than with Zispin.

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 theraphy or early after treatment discontinuation (see section 4.4)

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

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other Antidepressant
ATC code: NO6AX11.

Mirtazapine is a centrally active presynaptic α2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT1 receptors, because 5-HT2 and 5-HT3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking α2 and 5-HT2 receptors and the R(-) enantiomer by blocking 5-HT3 receptors.

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 ≈ 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

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 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 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
Povidone
Magnesium Stearate
Aminoalkyl Methacrylate Copolymer E
Aspartame (E951)
Citric acid, anhydrous
Crospovidone
Mannitol (E421)
Microcrystalline Cellulose (E460)
Natural and artifical orange flavour (No. SN027512)
Sodium Hydrogen Carbonate (E500)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the blister strips and outer carton of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Peel-to-open perforated blister strips of 6 tablets. Each pack contains 30 tablets (5 blister strips of 6 tablets) in an over-labelled cardboard carton.

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

G & A Licensing Limited
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/8/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 26th September 2008

10 DATE OF REVISION OF THE TEXT

October 2010