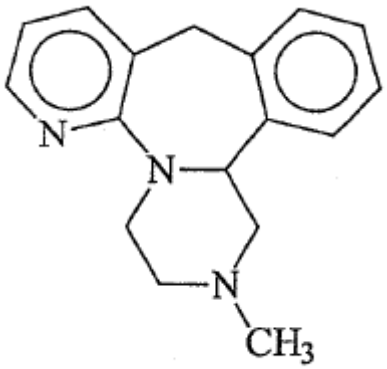
PRODUCT INFORMATION

MIRTAZAPINE SANDOZ® 15*/30/45mg FILM-COATED TABLETS

NAME OF THE MEDICINE
Active substance: mirtazapine



Mirtazapine INN name
Chemical name: (+/-)-1,2,3,4,10,14b- hexahydro-2-methyl- pyrazino[2,1-α] pyrido[2,3-c][2] benzazepine
CAS: 61337-67-5
Molecular formula: $C_{17}H_{19}N_3$. MW: 265.36

Pharmaceutical Form
Tablet

DESCRIPTION
Mirtazapine is a tetracyclic piperazinoazepine analogue of mianserin, a chemical structure unrelated to tricyclic antidepressants, MAOIs (monoamine oxidase inhibitors) or selective serotonin reuptake inhibitors. Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

Excipients: Core: lactose monohydrate, maize starch, hyprolose, colloidal anhydrous silica, magnesium stearate. Coating layer: hypromellose, macrogol 8000, titanium dioxide, and, as colouring agents: for the 15 mg strength: iron oxide yellow, quinolone yellow aluminium lake and sunset yellow FCF aluminium lake; for the 30mg strength: iron oxide red, iron oxide yellow and iron oxide black .

Qualitative and Quantitative Composition
The 15mg tablets contain 15mg mirtazapine, the 30mg tablets contain 30mg mirtazapine and the 45mg strength contains 45mg of mirtazapine.

PHARMACOLOGY

Pharmacodynamics:

Mirtazapine is an antidepressant, which can be given as treatment for episodes of major depression. Mirtazapine is an antagonist of central alpha$_2$-auto and hetero-adrenoceptors which causes an increase in both noradrenaline and serotonin release. The effect of released serotonin is exerted specifically via 5-HT$_1$ type receptors, because 5-HT$_2$ and 5-HT$_3$ type receptors are specifically blocked by mirtazapine. Mirtazapine is accordingly a noradrenergic and specific serotonergic antidepressant. The alpha$_2$, 5-HT$_2$ and 5-HT$_3$ antagonistic effects all contribute to the antidepressant profile of mirtazapine.

The presentation of mirtazapine is as a racemate. The two enantiomers contribute differently to its pharmacological profile. The alpha$_2$ and 5-HT$_2$ receptor blocking activity is contained in the (S)+ enantiomer, whereas the 5-HT$_3$ receptor blocking activity is contained in the (R)- enantiomer. The presence of both enantiomers is therefore considered to be essential for the antidepressant activity of mirtazapine. In one study, there was no efficacy difference indicated between the two enantiomers, despite their different receptor affinities.

Mirtazapine is generally well tolerated. The histamine H$_1$-antagonistic activity of mirtazapine may cause a degree of sedation in the first weeks of treatment. It has practically no anticholinergic activity. Mirtazapine has been associated with acute postural hypotension in healthy volunteer studies but this occurred rarely in patient studies (see ADVERSE EFFECTS).

Pharmacokinetics

Absorption. After oral administration of mirtazapine tablets, the active substance mirtazapine is rapidly and well absorbed (bioavailability approx. 50%), reaching peak plasma levels after about two hours. Food intake has no clinically significant influence on the pharmacokinetics of mirtazapine.

Distribution. Binding of mirtazapine to plasma proteins is approximately 85%. The half-life of elimination ranged from 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 elimination is sufficient to justify once-a-day-dosing. Steady state is reached after 3-6 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range.

Metabolism. 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 presentation of mirtazapine is as a racemate. It is not known whether first-pass extraction of the drug is stereoselective but it is known that the clearance of the two enantiomers is by different metabolic processes.

Elimination. Mirtazapine is extensively metabolized and its metabolites are eliminated via the urine and faeces within four days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. The dimethyl metabolite is

pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound.

Special populations
Renal and/or hepatic impairment. The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency. Mirtazapine is substantially excreted by the kidney (75%) and the risk of decreased clearance of this drug is greater in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Geriatric. The recommended dosage regimen is the same as for adults. Increases should be monitored carefully (see DOSAGE AND ADMINISTRATION).

Children and adolescents. The safety and effectiveness of mirtazapine have not been established in children and adolescents and therefore should not be prescribed in these patient groups (see PRECAUTIONS*).*

Sex. The half-life of elimination of mirtazapine ranged from 20 to 40 hours, longer half-lives up to 65 hours have occasionally been recorded and shorter half-lives have been seen in young men.

Race. There is no information available regarding the effect of race on the pharmacokinetics of mirtazapine.

CLINICAL TRIALS

Several placebo-controlled double-blind studies have demonstrated that mirtazapine is statistically significantly more effective than placebo in the short term treatment of a major depressive episode; the efficacy is maintained during continuation treatment with mirtazapine.

Active controlled studies
The efficacy of mirtazapine has been found to be comparable to several standard antidepressant agents (amitriptyline, doxepin, clomipramine). In addition, eleven 6 or 8 week studies and a 24 week study have been performed in moderately to severely depressed patients in which efficacy and tolerability of mirtazapine were compared to SSRIs (4 vs fluoxetine, 3 vs paroxetine, 2 vs sertraline, 2 vs fluvoxamine and 1 vs citalopram)> the primary efficacy parameters in these studies were:

- change from baseline on HAM-D total score (Hamilton depression rating scale, 17 items). 7 studies.
- proportion or number of HAM-D 50% responders. 3 studies.
- change from baseline on MADRAS total score (Montgomery-Asberg depression rating scale, 10 items). 1 study.
- VAMRS 6 items (Visual Analogue Mood Rating Scale). 1 study. Change in HAM-D (12 items) total score was a secondary parameter in this study.

On an intention-to-treat basis, a total of 1402 patients were treated with mirtazapine and 1405 patients were treated with the comparator. In all 12 studies, mirtazapine proved to be at least comparable in efficacy to the SSRIs. In 11 of these studies,

statistically significant greater reductions in HAM-D or MADRS total scores and more responders were observed in the mirtazapine groups at one or more time points in the first 4 weeks.

A meta-analysis of these 12 studies provides further comparison of the onset of efficacy of mirtazapine relative to the SSRIs studied. The primary efficacy parameter for this meta-analysis was time to first 50% reduction on recalculated HAM-D total score (17 items) or recalculated MADRS total score (10 items). There were also a number of secondary parameters which are identified in Tables 1 and 2. Table 1 provides an analysis of the relative event rates (estimated hazard ratios) for various depression parameters limited to the first 3 treatment weeks for the occurrence of the event and the entire 6-8 week study period to define whether the event was sustained or not. The increased hazard ratios demonstrate that the probability at any time t of first response (50% or more score reduction), remission, sustained response or sustained remission was consistently and significantly greater among mirtazapine-treated than SSRI-treated patients, indicating an earlier onset of efficacy. The statistically earlier onset of action observed with mirtazapine may not necessarily translate in to a meaningful clinical benefit for an individual patient. Table 2 presents the proportions of HAM-D responders and HAM-D/MADRS remitters at the various time points during treatment. At most time points there were significantly more responders and remitters among mirtazapine-treated patients than among SSRI-treated patients.

Table 1

Parameter * primary ** secondary	**Estimated hazard ratio mirtazapine relative to SSRI.**	**95% confidence interval**	**p-value**
first day 50% or more reduction in HAM-D/MADRAS total score *	1.49	1.32 - 1.68	≤ 0.001
first day 50% reduction on HAM-D Bech depression factor **	1.20	1.06 – 1.37	0.005
day of 50% or more sustained reduction in HAM-D/MADRAS total score **	1.58	1.37 – 1.82	≤ 0.001
day of 50% sustained reduction on HAM-D Bech depression factor **	*1.22*	*1.05 – 1.42*	*0.010*
first day remission on HAM-D total score (≤ 7) or MADRAS total score (≤ 12) **	1.67	1.40 – 2.00	≤ 0.001
day of sustained remission on HAM-D total score (≤ 7) or MADRAS total score (≤ 12) **	1.68	1.35 – 2.09	≤ 0.001

Table 2

Parameter * primary ** secondary	**Cumulative probability mirtazapine (%) v SSRI (%)** **(Estimated Difference (%) between mirtazapine and SSRI adjusted for trial)** **(p value)**				
	Week 1	Week 2	Week 4	Week 6	EP***
HAM-D responders * (subjects where score is reduced by ≥ 50%)	11.5 v 7.0 (4.4) (≤ 0.001)	29.5 v 20.8 (8.6) (≤ 0.001)	50.4 v 40.7 (9.7) (≤ 0.001)	60.2 v 55.1 (5.2) (0.013)	61.5 v 57.1 (4.4) 0.023)
MADRS responders * (subjects where score is reduced by ≥ 50%)	6.6 v 4.7 (1.9) (0.205)	28.8 v 20.1 (8.6) (0.002)	51.6 v 49.0 (2.5) (0.455)	65.3 v 65.3 (-0.1) (0.967)	72.4 v 73.2 (-0.9) (0.768)
HAM-D or MADRS responders * (subjects where score is reduced by ≥ 50%)	10.5 v 6.6 (3.9) (≤ 0.001)	28.7 v 20.3 (8.3) (≤ 0.001)	51.5 v 42.2 (9.3) (≤ 0.001)	61.9 v 57.4 (4.6) (0.018)	63.8 v 60.0 (3.7) (0.038)
HAM-D or MADRAS remitters ** (HAM-D ≤ 7 MADRS ≤ 12)	3.4 v 1.8 (1.6) (0.008)	11.8 v 6.9 (4.9) (≤ 0.001)	28.6 v 21.8 (6.8) (≤ 0.001)	38.8 v 34.7 (4.1) (0.028)	42.7 v 39.9 (2.7) (0.126)

The shaded cells indicate statistical significance in the result.
*** EP – Endpoint analysis consists of results from week 6 assessments of the 6 week studies and week 8 assessments of the 8 week studies.

Some secondary parameter results have been excluded from Table 2. These were number of:

- 50% Bech responders
- 50% HAM-D Factor I ‘anxiety/somatisation’ responders
- 50% HAM-D Factor V ’retardation’ responders
- 50% HAM-D Factor VI ’sleep disturbance’ responders
- HAM-D item ‘depressed mood’ responders (= 0 or <2)
- HAM-D item ‘suicide or MADRS item ‘suicidal thoughts’ (= 0 or <2)

Statistically significant differences favouring mirtazapine were observed for HAM-D factors V and VI at week 1 to 6 time points. Statistically significant differences favouring mirtazapine were observed for HAM-D factor I at week 1 to 4 time points. A statistically significant difference was observed in favour of mirtazapine for Bech responders at the week 2 time point. There were no other statistically significant differences.

An eight-week comparative study was performed to compare the antidepressant efficacy and tolerability of mirtazapine and venlafaxine in the treatment of 157 hospitalised patients with severe depression with melancholic features (HAM-D total score > 25). In this study, mirtazapine and venlafaxine were equally effective in reducing symptoms of depression and improving quality of life during treatment.

Long-term maintenance of efficacy and relapse prevention

The long term maintenance of antidepressant efficacy of mirtazapine was originally established in three active-controlled and active/placebo-controlled studies with treatment periods up to 24 months (amitriptyline as active). Long term maintenance of efficacy was also confirmed in extension phases of 3 SSRI comparator studies, a 24 week paroxetine comparator study and 1 venlafaxine comparator study. Additionally, a multicentre, long-term, double-blind, placebo-controlled study of relapse prevention in male and female outpatients diagnosed with moderate to severe recurrent major depression (Protocol 003041) was performed. In the initial open-label phase of the study, 421 patients were treated with mirtazapine for 8-12 weeks. Patients remitting after 8-12 weeks were randomised into the 40-week, double blind, relapse prevention phase of the study. The remitted patients were randomised to either mirtazapine at the final titrated dose they received during the open-label phase or placebo (79 to mirtazapine and 81 to placebo). The results of the trial showed that mirtazapine reduced the risk of relapse by more than half (15/76=19.7% relapsed on mirtazapine versus 35/80=43.8% relapsed on placebo, p = 0.001). The treatment was well-tolerated with dropouts due to adverse events being 11.4% (9/79) from the mirtazapine group and 2.5% (2/81) from the placebo group. Further discontinuation details are summarised below in Table 3.

Table 3: Summary of reasons for discontinuation from relapse prevention study

	mirtazapine %	placebo %
Relapse	**19.7**	**43.8**
(Serious) adverse events	11.4	2.5
Lost to follow up	19.0	14.8
Other	17.7	17.3

Elderly
The efficacy and tolerability in elderly patients was investigated in three randomised controlled trials. In two six-week trials with a total of 270 patients aged over 55 years (mean age 70 and 62 years respectively), mirtazapine was at least as effective as amitriptyline and all treatments were well tolerated. In an eight-week study in 255 patients aged 65 and over (mean age 72 years) comparing mirtazapine with paroxetine, mean HAM-D scores were similar at end-point but lower for mirtazapine in the first 3 weeks, although only at day 14 was the difference statistically significant. Total discontinuation rates were similar (22.7% for mirtazapine versus 31.0% for paroxetine), although discontinuation due to adverse events was lower with mirtazapine than paroxetine (14.8% versus 26.2%) and discontinuation due to lack of efficacy higher (3.9% versus 0%).

INDICATIONS
Treatment of major depression

CONTRAINDICATIONS

Hypersensitivity to mirtazapine or to any of the excipients.

Monoamine oxidase inhibitors (MAOIs) as concomitant therapy. It is recommended that Mirtazapine Sandoz not be used in combination with MAOIs or within 14 days of initiating or discontinuing therapy with an MAOI. (see INTERACTIONS WITH OTHER MEDICINES**)**

PRECAUTIONS

Clinical worsening and suicide risk.

The risk of suicidality (suicidal ideation and suicidal behaviour) is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and/or behaviours whether or not they are taking antidepressant medication and this risk may persist until significant remission occurs. Suicide is a known risk in depression and certain other psychiatric disorders themselves are the strongest predictors of suicide.

As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation or behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increased the risk of suicidal ideation and/or behaviours in children, adolescents, and young adults (aged 18-24 years) with major depressive disorder (MDD) and other psychiatric disorders during the initial treatment (generally the first one to two months). Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

The pooled analysis of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials (4 to 16 week) of nine antidepressants medicines (SSRIs and others) in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term

trials (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but there was a tendency towards an increase in the younger patients for almost all antidepressants studied. There were differences in absolute risk of suicidality across different indications, with the highest incidence in MDD trials. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications.

No suicides occurred in any of the paediatric trials. There were few suicides in the adult trials, but the number was not sufficient to reach any conclusion about the effect of antidepressants on suicide. It is unknown whether suicidality risk extends to longer-term use, i.e. beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorders as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressants treatment or at times of dose increase or decrease.

Prescriptions for Mirtazapine Sandoz should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

<u>Conditions which need supervision</u>

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

- epilepsy and organic brain syndrome (see ADVERSE EFFECTS): 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
- renal insufficiency. Mirtazapine is substantially excreted by the kidney (75%) and the risk of decreased clearance of this drug is greater in patients with impaired renal function.

- 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 and conditions that would predispose patients to hypotension (dehydration, hypovolaemia and treatment with antihypertensive medication)
- diabetes mellitus: In patients with diabetes, antidepressants may alter glycemic control. Insulin and/or oral hypoglycemic dosage may need to be adjusted and close monitoring is recommended.

Like with other antidepressants, the following should also be taken into account:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because mirtazapine possesses only very weak anticholinergic activity)
- acute narrow-angle glaucoma and increased intraocular pressure (however mirtazapine has weak anticholinergic activity)
- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances, paranoid thoughts can be intensified
- a major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression. When the depressive phase of the 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.
- akathisia/psychomotor restlessness: The use of antidepressants have been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.
- Mirtazapine Sandoz is not addictive. Postmarketing 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, nausea, headache, anxiety and agitation 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 DOSAGE AND ADMINISTRATION, it is recommended to discontinue treatment with mirtazapine gradually.

Jaundice
Treatment should be discontinued if jaundice occurs.

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
Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAO-Is (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES) or other serotonergic agents (see Interactions with other medicines). Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), hyperthermia, rigidity, myoclonus, mental status changes that include extreme altered mental status (confusion, irritability, agitation, hypomania and agitation progressing to delirium and coma) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine. Treatment with mirtazapine should be discontinued if such events occur and supportive symptomatic treatment initiated. From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with mirtazapine alone (see ADVERSE EFFECTS).

Neutropenia, agranulocytosis.
Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with mirtazapine. The symptoms mostly appear after two to six weeks of treatment. The bone marrow depression is, in general, reversible after termination of treatment. However in very rare cases agranulocytosis can be fatal. Reversible agranulocytosis has been reported as a rare occurrence in clinical studies with mirtazapine. In 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 over 65 years. Post-marketing data indicate that the rate of occurrence of agranulocytosis and agranulocytosis-like disorders (whether or not causally related) amongst mirtazapine users is no greater than in the background population. One should therefore be alert for symptoms like fever, sore throat, stomatitis or other signs of infections. If such symptoms occur the treatment should be stopped and blood counts taken.

Excipients. The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not receive this medicine.

Effects on fertility
In a fertility study in rats, mirtazapine was given at doses up to 100mg/kg (about 20 times the recommended human dose of 45mg on a mg/m^2 basis). The drug did not affect mating and conception, but oestrus cycling was disrupted at doses that were three or more times the recommended human dose of 45mg on a mg/m^2 basis.

Use in pregnancy
Australian Pregnancy Category B3_Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

There are insufficient clinical data to assess the possible effect of mirtazapine on pregnancy.

Oral dosing of pregnant rats with mirtazapine at 100mg/kg/day was associated with a reduction in survival of the offspring, and an increased incidence of postnatal mortality. Mirtazapine was not teratogenic in rats at these dose levels, or in rabbits at oral doses up to 40mg/kg/day.

Although studies in animals have not shown any teratogenic effects of toxicological significance the safety of mirtazapine in human pregnancy has not been established. Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to mirtazapine treatment, this potential risk cannot be ruled out taking into account the related mechanism of action (increase in serotonin concentrations). Mirtazapine should be used during pregnancy only if it is clearly needed. Women of childbearing potential should employ an adequate method of contraception if taking mirtazapine .

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

Use in lactation
Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, postnatal mortality was increased when lactating rats were given mirtazapine orally at 100mg/kg/day.
The use of mirtazapine in breastfeeding mothers is not recommended since no human data in breast milk are available.

Use in children and adolescents (<18 years of age)
Mirtazapine should not be used to treat 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.

Use in the elderly
Elderly patients are often more sensitive, especially with regard to the undesirable side effects of antidepressants. During clinical research with mirtazapine, side effects have not been reported more often in elderly patients than in other age groups; however experience until now is limited (see also CLINICAL TRIALS AND DOSAGE AND ADMINSTRATION).

Genotoxicity
Mirtazapine was not genotoxic in a series of tests for gene mutation and chromosomal and DNA damage.

Carcinogenicity and mutagenicity
An 18 month carcinogenicity study in mice showed an increase in the development of hepatic tumours in males after mirtazapine treatment at oral doses of 20mg/kg/day and above. In a two year carcinogenicity study in rats, oral doses of mirtazapine greater than 20mg/kg/day were associated in males with an increased incidence of thyroid follicular cell adenomas and carcinomas.

Since the only tumours found in carcinogenicity studies with mice and rats were considered to be species specific, non-genotoxic responses associated with long-term treatment with hepatic enzyme inducers, mirtazapine is not expected to possess carcinogenic potential at therapeutic dosages in the clinic.

Effect on ability to drive or operate machinery.
Mirtazapine may impair concentration and alertness (more commonly in the initial phase of treatment). Patients treated with mirtazapine should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the treatment does not affect them adversely.

INTERACTIONS WITH OTHER MEDICINES

Pharmacokinetic interactions:

Mirtazapine is extensively metabolised by CYP2D6 (resulting in the 8-hydroxy metabolite) and CYP3A4 (N-demethyl and N-oxide metabolites) and to a lesser extent by CYP1A2. An interaction study with healthy volunteers showed no influence of paroxetine, a CYP2D6 inhibitor, on mirtazapine pharmacokinetics in steady state.

Caution is needed when strong CYP3A4 inhibitors, such as the HIV protease inhibitors, azole antifungals, ketoconazole, erythromycin and nefazodone are coadministered with mirtazapine. Co-administration of ketoconazole, a potent CYP3A4 inhibitor, in healthy male volunteers increased mirtazapine peak plasma concentration levels and AUC by approximately 40% and 50% respectively.

Carbamazepine and phenytoin, inducers of CYP3A4, increased mirtazapine clearance about twofold, resulting in a decrease in plasma levels of 45 to 60%. When carbamazepine, phenytoin or another inducer of drug metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with an inducer is stopped, the mirtazapine dose may have to be decreased.

When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration of mirtazapine may increase more than 50%. The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started or increased when cimetidine treatment is ended. 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, ketoconazole, erythromycin, cimetidine or nefazodone.

In *in vivo* interaction studies, mirtazapine did not influence the pharmacokinetics of paroxetine (CYP2D6 substrates), carbamazepine or phenytoin (CYP3A4 inducers), amitriptyline or cimetidine.

In a mirtazapine and lithium interaction study, the steady state pharmacokinetics of lithium was not affected by co-administration of a single oral dose of 30mg of mirtazapine. Correspondingly, the single dose pharmacokinetics of mirtazapine was not affected by the lithium steady state.

Pharmacodynamic interactions:

Mirtazapine should not be administered concomitantly with monoamine oxidase (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 CONTRAINDICATIONS). 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 (see PRECAUTIONS). Caution should be advised and a closer clinical monitoring is required when these active substances are combined with mirtazapine.

Mirtazapine may potentiate the sedative effects of benzodiazepines and other sedatives (especially antipsychotics, antihistamine H1 antagonists, opioids); caution should be taken when these drugs are prescribed together with mirtazapine.

Mirtazapine may potentiate the central nervous dampening action of alcohol; patients should therefore be advised to avoid alcohol during treatment with Mirtazapine for tasks which require concentration and alertness.

Mirtazapine dosed at 30mg daily caused a small but statistically significant increase of the INR in subjects treated with warfarin. Both at continuing stable doses and higher doses of mirtazapine, a more pronounced effect cannot be excluded. It is advisable to monitor the prothrombin time more carefully in case of concomitant treatment of warfarin with mirtazapine.

From post marketing experience it appears that serotonin syndrome occurs very rarely in patients treated with mirtazapine in combination with SSRIs or venlafaxine. If the combination is considered therapeutically necessary, dosage changes should be made with caution and there should be adequate close monitoring for early signs of serotonergic overstimulation.

ADVERSE EFFECTS

Clinical Trials. 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.

System Organ Class	**Common ≥ 1/100 to < 1/10 (≥ 1% and < 10%)**	**Uncommon ≥1/1,000 to < 1/100 (≥ 0.1% and < 1%)**	**Rare ≥ 1/10,000 to < 1/1,000 (≥ 0.01% and < 0.1%)**	**Very Rare < 1/10,000**	**Frequency not known**
Blood and the lymphatic system disorders			granulocytopenia agranulocytosis		Bone marrow depression aplastic anaemia, thrombocytopenia, Eosinophilia
Endocrine disorders					Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Increase in appetite Weight increased				Hyponatraemia
Psychiatric disorders	Abnormal dreams Confusion Anxiety Insomnia	Agitation Hallucinations Psychomotor restlessness (incl. akathisia, hyperkinesia)	Aggression Mania Nightmares/ vivid dreams (paroniria)	suicidal ideation/ behaviour	
Nervous system disorders	Drowsiness/ sedation generally occurring during the first weeks Lethargy Somnolence	Dizziness Headache Syncope	Epileptic seizures Tremor Convulsions (insults) myoclonus Paraesthesia Restless legs (hyperkinesia)		Serotonin syndrome Oral paraesthesia Dysarthria
Vascular disorders		Hypotension	Orthostatic hypotension		
Gastrointestinal Disorders	Dry mouth Nausea Diarrhoea Vomiting	Oral hypoaesthesia			Mouth oedema Increased salivation
Hepatobiliary Disorders		Elevations in serum transaminase activities			
Skin and subcutaneous tissue disorders			exanthema		Stevens-Johnson Syndrome Dermatitis bullous Erythema multiforme Toxic epidermal necrolysis
Musculoskeletal Connective Tissue and Bone Disorders	Back pain		arthralgia myalgia		
General disorders and administration site conditions	Generalised or local oedema Oedema peripheral Fatigue				Somnambulism
Investigations	Weight gain				

Post-marketing reports

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis, rare cases of increased sweating, alopecia, pruritus and urticaria.

Musculoskeletal connective tissue and bone disorders: back pain, arthralgia, myalgia.

Nervous system disorders: lethargy, dysarthria, somnolence (i.e.drowsiness, sedation), serotonin syndrome, impaired concentration, dizziness, paraesthesia, headache, hyperkinesia, rare cases of cerebrovascular disorder, convulsions, tremor and myoclonus, movement disorders **, very rare cases of oral paraesthesia.

Psychiatric disorders: suicidal ideation***, suicidal behaviour***, confusion, agitation, aggression, paroniria, less common or rare occurrences of nightmares/vivid dreams, hallucination, mania, depression, anxiety*, insomnia* and psychomotor restlessness**.

Gastrointestinal disorders: nausea, diarrhoea, dry mouth, less common or rare cases of stomatitis; very rare cases of oral hypoaesthesia and mouth oedema.

Hepatobiliary disorders: hepatic function abnormality, elevated hepatic enzymes or transaminases, rare cases of jaundice, hepatitis.

Metabolism and nutrition disorders: increased appetite, hyponatraemia, rare cases of hypercholesterinaemia, hyperlipidaemia.

Cardiac disorders: tachycardia, palpitation (rare), arrhythmia , myocardial infarction, chest pain.

Vascular disorders: hypotension, dependant oedema, hypertension, orthostatic hypotension, rare cases of thromboembolic disorder, pulmonary embolism.

Blood and lymphatic system disorders: leucopenia, granulocytopenia, rare cases of agranulocytosis (see PRECAUTIONS), rare cases of thrombocytopenia, pancytopenia, anaemia, aplastic anaemia, eosinophilia and coagulation disorder.

Renal and urinary disorders: rare cases of urinary retention.

General disorders and administration site conditions: oedema including generalised, peripheral and facial oedema; fatigue/ asthenia, rare cases of pyrexia, syncope, chest pain and withdrawal symptoms.

Investigations. increase in gamma-glutamyltransferase levels, hypertriglyceridaemia, weight gain.

Eye disorders: very rare cases of glaucoma.

*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 very rarely

**Including akathisia, hyperkinesia.

***Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation (see PRECAUTIONS, Clinical worsening and suicide risk).

DOSAGE AND ADMINISTRATION

The tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Adults. Treatment should begin with 15mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 30 and 45mg, but responses have been observed at 60mg per day.

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

Use in patients with hepatic and/ or renal impairment.
The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Mirtazapine Sandoz to this category of patients (see PRECAUTIONS and PHARMACOLOGY, Pharmacokinetics sections).

Mirtazapine has a half-life of 20 to 40 hours and therefore mirtazapine is suitable for once a day administration. It should be taken preferably as a single night-time dose before going to bed. Mirtazapine may also be given in subdoses 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 four to six months. After this, treatment can be gradually discontinued to avoid withdrawal symptoms (see PRECAUTIONS). 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 two to four weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further two to four weeks, then treatment should be stopped.

Use in Children and Adolescents (< 18 years of age) In placebo controlled trials, safety and efficacy of mirtazapine 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, mirtazapine should not be used in children and adolescents under the age of 18 years.

OVERDOSAGE

Post-marketing experience concerning overdose with mirtazapine alone indicates that symptoms are usually mild. The symptoms of overdose are an exaggeration of the pharmacological action of mirtazapine and may include symptoms such as dizziness,

impaired consciousness (confusion, disorientation, stupor, coma), agitation, tremor, tachycardia and hyper- and hypotension.

As with all overdose attempts, the possibility of multiple drug ingestion should be borne in mind. As with antidepressants in general, serious outcomes, including fatalities, are possible at dosages much higher than the therapeutic dose, especially with mixed overdoses.

Overdose management

Cases of overdose should receive appropriate and supportive therapy for vital functions.

Contact the Poison Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Mirtazapine Sandoz 15mg* tablets: Yellow, film-coated tablets, round, biconvex, one sided score notch. Available in blisters (PVC/PVDC/Al) of 30 tablets and bottles (HDPE with Polypropylene/Polyethylene child resistant closure)* of 30 or 60 tablets.
The 15mg tablets contain 15mg mirtazapine.
Mirtazapine Sandoz 30mg tablets: Beige, film-coated tablets, round, biconvex, one sided score notch. Available in blisters (PVC/PVDC/Al) of 30 or *60 tablets and bottles (HDPE with Polypropylene/Polyethylene child resistant closure)* of 30 or 60 tablets.
The 30mg tablets contain 30mg mirtazapine.
Mirtazapine Sandoz 45mg tablets: White, film-coated tablets, circular, biconvex. Available in blisters (PVC/PVDC/Al) of 30 or *60 tablets and bottles (HDPE with Polypropylene/Polyethylene child resistant closure)* of 30 or 60 tablets.
The 45mg tablets contain 45mg mirtazapine.

* Not currently marketed in Australia

Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road,
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 19/06/2006

Date of most recent amendment: 10/06/2016