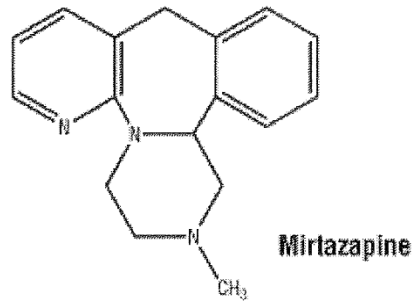


**APO-MIRTAZAPINE TABLETS****NAME OF THE MEDICINE**

Mirtazapine

Chemical Name: ( $\pm$ )-1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine.

Structural Formula:

Molecular Formula:  $C_{17}H_{19}N_3$ 

Molecular Weight: 265.36

CAS Registry Number: 61337-67-5

**DESCRIPTION**

Mirtazapine is a white to creamy white crystalline powder which is slightly soluble in water.

Each mirtazapine tablet contains mirtazapine as the active ingredient. In addition, each tablet contains the following inactive ingredients: lactose, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, hypromellose, hydroxypropylcellulose, macrogol 8000, titanium dioxide, iron oxide yellow CI 77492 (15 mg and 30 mg), iron oxide red CI 77491 (30 mg only).

**PHARMACOLOGY**

Mirtazapine is a tetracyclic piperazinoazepine analogue to mianserin, a chemical structure unrelated to tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs).

**Pharmacological Actions**

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).

The results of three pivotal placebo-controlled double-blind studies (161 patients received placebo and 161 patients received mirtazapine) 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 of treatment with mirtazapine. The efficacy of mirtazapine has been found to be comparable to several standard antidepressant agents (amitriptyline, doxepin, clomipramine). As of 1996 no comparative studies have been performed with SSRIs or mianserin (to which mirtazapine has structural similarities).

## Pharmacodynamics

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<sub>1</sub> type receptors, because 5-HT<sub>2</sub> and 5-HT<sub>3</sub> type receptors are specifically blocked by mirtazapine.

Both the enantiomers of mirtazapine are presumed to contribute to the antidepressant activity, the S(+) enantiomer by blocking  $\alpha_2$ -auto and hetero-adrenoceptors and 5-HT<sub>2</sub> receptors and the R(-) enantiomer by blocking  $\alpha_2$  hetero-adrenoceptors and 5-HT<sub>3</sub> receptors. In one study, there was no efficacy difference indicated between the two enantiomers, despite their different receptors affinities.

Mirtazapine is generally well tolerated. The histamine H<sub>1</sub>-antagonistic activity of mirtazapine may cause a degree of sedation in the first few 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 ~ 50%), reaching peak plasma levels after about 2 hours.

Food intake has no clinically significant influence on the pharmacokinetics of mirtazapine.

### Distribution

Binding of mirtazapine to plasma proteins is approx. 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 of 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 metabolised 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 demethyl 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, refer to **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 has not been established in children and adolescents and therefore should not be prescribed in these patient groups (see **PRECAUTIONS**).

### *Sex*

The half-life elimination of mirtazapine ranged from 20–40 hours, longer half-lives of 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.

## **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 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 behaviours) is inherent in depression and may persist until significant remission occurs. The 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, and these 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 analysis of short-term placebo-controlled trials of antidepressant drugs [selective serotonin reuptake inhibitors (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 disorders (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 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 weeks) of 9 antidepressant drugs 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 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in the risk of suicidality among drugs, but a tendency towards an increase in the younger patients for almost all drugs 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 disorders 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 healthcare providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

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

### Conditions which need supervision

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

- **Epilepsy and organic brain syndrome** (see **ADVERSE EFFECTS**). Mirtazapine should be introduced cautiously in patients who have had 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.** Such as 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 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 also 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.

- 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.
- Care should be taken in patients with 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 intra-ocular pressure (however mirtazapine has 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.
- Cases of QT prolongation, *Torsades de Pointes*, ventricular tachycardia, and sudden death, have been reported during the post-marketing use of mirtazapine. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc prolonging medicines (**see INTERACTION WITH OTHER MEDICINES** and **OVERDOSAGE** sections). Caution should be exercised when mirtazapine is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval.
- 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 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 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), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). 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**).

### Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Neutropenia, Agranulocytosis**

Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with mirtazapine. The symptoms mostly appear after 2–6 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 the post-marketing period with mirtazapine, very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. All fatal cases concerned patients 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 that 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.

**Effects on Fertility**

In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (ca. 20 times the recommended human dose of 45 mg on a mg/m<sup>2</sup> basis). The drug did not affect mating and conception, but oestrus cycling was disrupted at doses that were 3 or more times the recommended human dose of 45 mg on a mg/m<sup>2</sup> basis.

**Use in Pregnancy (Category B3)**

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

Oral dosing of pregnant rats with mirtazapine at 100 mg/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 40 mg/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 child-bearing potential should employ an adequate method of contraception if taking mirtazapine.

**Use in Lactation**

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, post-natal mortality was increased when lactating rats were given mirtazapine orally at 100 mg/kg/day.

The use of mirtazapine in breastfeeding mothers is not recommended since no human data in breast milk are available.

**Paediatric Use (< 18 years)**

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 behaviours 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 effects of antidepressants. During clinical research with mirtazapine, undesirable effects have not been reported more often in elderly patients than in other age groups. (Refer to **DOSAGE AND ADMINISTRATION**).

### Carcinogenicity

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

### Genotoxicity

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.

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

### Effects 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.
- Co-administration of the potent inhibitor of CYP3A4, ketoconazole, in healthy male volunteers increased mirtazapine peak plasma concentration levels and AUC 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%. 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.
- Carbamazepine and phenytoin, inducers of CYP3A4, increased mirtazapine clearance about two-fold, resulting in a decrease in mirtazapine plasma levels of 45–60%. 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.
- 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 were not affected by co-administration of a single oral dose of 30 mg mirtazapine. Correspondingly, the single dose pharmacokinetics of mirtazapine were not affected by the lithium steady state.

### 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 **CONTRAINDICATIONS**). In addition, as with SSRIs, co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, methylene blue, 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 H<sub>1</sub> 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 using mirtazapine should therefore be advised to avoid alcohol during tasks which require concentration and alertness.
- Mirtazapine dosed at 30 mg 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.
- The risk of QT prolongation and/or ventricular arrhythmias (e.g. *Torsades de Pointes*) may be increased with concomitant use of medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics) and in case of mirtazapine overdose.

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 CLASS	ORGAN	COMMON (> 1/100 to < 1/10)	UNCOMMON (> 1/1000 to ≤ 1/100)	RARE (> 1/10,000 to ≤ 1/1000)
Blood & Lymphatic System Disorders				<ul style="list-style-type: none"> <li>• Granulocytopenia</li> <li>• Agranulocytosis</li> </ul>
Metabolism & Nutrition Disorders		<ul style="list-style-type: none"> <li>• Increase in appetite</li> </ul>		
Psychiatric Disorders				<ul style="list-style-type: none"> <li>• Mania</li> <li>• Nightmares/vivid dreams (paroniria)</li> </ul>



SYSTEM CLASS	ORGAN	COMMON (> 1/100 to < 1/10)	UNCOMMON (> 1/1000 to ≤ 1/100)	RARE (> 1/10,000 to ≤ 1/1000)
<b>Nervous System Disorders</b>		<ul style="list-style-type: none"> <li>Drowsiness/sedation generally occurring during the first weeks</li> </ul>	<ul style="list-style-type: none"> <li>Dizziness</li> <li>Headache</li> </ul>	<ul style="list-style-type: none"> <li>Epileptic seizures</li> <li>Tremor</li> <li>Convulsions (insults)</li> <li>Myoclonus</li> <li>Paraesthesia</li> <li>Restless legs (hyperkinesia)</li> </ul>
<b>Vascular Disorders</b>				<ul style="list-style-type: none"> <li>Orthostatic hypotension</li> </ul>
<b>Hepatobiliary Disorders</b>			<ul style="list-style-type: none"> <li>Elevations in serum transaminase activities</li> </ul>	
<b>Skin &amp; Subcutaneous Tissue Disorders</b>				<ul style="list-style-type: none"> <li>Exanthema</li> </ul>
<b>Musculoskeletal Connective Tissue &amp; Bone Disorders</b>				<ul style="list-style-type: none"> <li>Arthralgia</li> <li>Myalgia</li> </ul>
<b>General Disorders &amp; Administration Site Conditions</b>		<ul style="list-style-type: none"> <li>Generalized or local oedema</li> </ul>		
<b>Investigations</b>		<ul style="list-style-type: none"> <li>Weight gain</li> </ul>		

### Post-Marketing Reports

#### Skin and Subcutaneous Tissue Disorders

Steven-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis, rash (including erythematous and maculopapular).

Rare cases of increased sweating, alopecia, pruritus and urticaria.

#### Musculoskeletal Connective Tissue and Bone Disorders

Back pain, arthralgia, myalgia.

#### Nervous System Disorders

Lethargy, dysarthria, serotonin syndrome, somnolence (i.e. drowsiness sedation), 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

Constipation, vomiting, pancreatitis, increased salivation, nausea, diarrhoea, dry mouth.  
Less common or rare cases of stomatitis.  
Very rare cases of oral hypoaesthesia and mouth oedema.

#### Hepatobiliary Disorders

Hepatic function abnormal, elevated hepatic enzymes or transaminases.  
Rare cases of jaundice, hepatitis.

#### Metabolism and Nutritional Disorders

Hyponatraemia, increased appetite, rare cases of hypercholesterolaemia, hyperlipidaemia.

#### Cardiac Disorders

Tachycardia, palpitations.  
Rare cases of arrhythmia, myocardial infarction, chest pain.

#### Vascular Disorders

Hypotension, dependent oedema, hypertension, orthostatic hypotension.  
Rare cases of thromboembolic disorder, pulmonary embolism.

#### Blood and Lymphatic System Disorders

Leukopenia, 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 face oedema, fatigue/asthenia.  
Rare cases of pyrexia, syncope, chest pain and drug withdrawal symptoms.

#### Investigation

Increases 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**)

### **DOSAGE AND ADMINISTRATION**

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

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

**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.

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

Mirtazapine has a half-life of 20–40 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 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 to avoid withdrawal symptoms. Mirtazapine generally begins to exert its effect 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.

#### **Paediatric Use (< 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**

### **Symptoms**

Post-marketing experience concerning overdose with mirtazapine alone indicates that symptoms are usually mild. The symptoms of overdose are an exaggeration of the pharmacological actions of mirtazapine and may include symptoms such as dizziness, impaired consciousness (confusion, disorientation, stupor, coma), agitation, tremor and tachycardia, hypertension and hypotension.

As with all overdose attempts, the possibility of multiple drug ingestion should be borne in mind.

As with other antidepressants in general, serious outcomes, including fatalities, are possible at dosages much higher than the therapeutic dose, especially with mixed overdoses.

### **Treatment**

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

ECG monitoring should be undertaken.

**For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).**

## **PRESENTATION AND STORAGE CONDITIONS**

APO-Mirtazapine Tablets are intended for oral administration.

Each tablet contains 15, 30 or 45 mg mirtazapine (as mirtazapine hemihydrate).

### **APO-MIRTAZAPINE 15 mg Tablets**

Pale Yellow, oval shaped, scored, film coated tablets, imprinted "APO" on one side and "M1" bisect "15" on the other side.

Blister pack (Clear PVC/PVdC Aluminium silver foil) of 30 tablets (AUST R 127666).

: Bottle (white, round HDPE bottle with blue PP Lift N Peel) of 30 tablets (AUST R 127662)

**APO-MIRTAZAPINE 30 mg Tablets**

Light pink, oval shaped, scored, film coated tablets, imprinted “APO” on one side and “MI” bisect “30” on the other side.

Blister pack (Clear PVC/PVdC Aluminium silver foil) of 30 tablets (AUST R 127678).

Bottle (white, round HDPE bottle with blue PP Lift N Peel) of 30 tablets (AUST R 127677)

**APO-MIRTAZAPINE 45 mg Tablets**

White to off-white, oval shaped, unscored, film coated tablets, imprinted “APO” on one side and “MI-45” on the other side.

Blister pack (Clear PVC/PVdC Aluminium silver foil) of 30 tablets (AUST R 127685).

Bottle (white, round HDPE bottle with blue PP Lift N Peel) of 30 tablets (AUST R 127684)

\* Not all strengths, pack types and/or pack sizes may be available.

**Storage**

Store below 30°C. Store in original package.

**NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd  
16 Giffnock Avenue  
Macquarie Park NSW 2113

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**POISON SCHEDULE OF THE MEDICINE**

S4 – Prescription Only Medicine.

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 10 August 2007

**DATE OF MOST RECENT AMENDMENT:** 28 January 2016