SINGAPORE PACKAGE INSERT

PrAPO-MIRTAZAPINE

Mirtazapine Tablets

USP

15 mg, 30 mg and 45 mg

Antidepressant

DATE OF PREPARATION:
October 02, 2006
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February 02, 2011

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[Pr]APO-MIRTAZAPINE
Mirtazapine Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 15 mg , 30 mg, 45 mg	Lactose Monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APO-MIRTAZAPINE (mirtazapine) is indicated for the symptomatic relief of depressive illness.

The efficacy of mirtazapine in maintaining a response in patients with major depressive disorder for up to 40 weeks following 8 - 12 weeks of initial open-label treatment was demonstrated in a placebo-controlled trial.

APO-MIRTAZAPINE (mirtazapine) is not indicated for use in children under the 18 years of age (See WARNINGS AND PRECAUTIONS: Potential Association With Behavioural And Emotional Changes, Including Self-Harm)

CONTRAINDICATIONS

APO-MIRTAZAPINE (mirtazapine) tablets are contraindicated in patients with a known hypersensitivity to mirtazapine and its excipients.

WARNINGS AND PRECAUTIONS

Potential Association With Behavioural And Emotional Changes, Including Self-Harm

Pediatrics: Placebo-Controlled Clinical Trial Data

- Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of

suicidal ideation and behaviour over that of placebo.

Adults and Pediatrics: Additional Data

- There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization, in some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms

Patients currently taking mirtazapine should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation, is recommended.

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

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

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

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

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

Treatment should be discontinued if jaundice occurs.

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

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified
- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase
- with regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of mirtazapine tablets should be given to the patient
- although mirtazapine is not addictive, post-marketing experience shows that abrupt termination of treatment after long term administration may sometimes result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea are the most frequently reported. Even though they have been reported as withdrawal symptoms, it should be realized that these symptoms may be related to underlying disease. As advised in section 4.2, it is recommended to discontinue treatment with mirtazapine gradually.
- elderly patients are often more sensitive, especially with regard to the undesirable effects of antidepressants. During clinical research with mirtazapine, undesirable effects have not been reported more often in elderly patients than in other age groups.
- from postmarketing experience it appears that serotonin syndrome occurs very rarely in patients treated with mirtazapine alone.
- interactions with other serotonergic drugs

Discontinuation of Treatment with APO-MIRTAZAPINE:

When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation (e.g. dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see ADVERSE REACTIONS). A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Use in patients with concomitant illness: Clinical experience with mirtazapine in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing APO-MIRTAZAPINE for patients with diseases or conditions that affect metabolism or hemodynamic responses. Mirtazapine has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. Mirtazapine was associated with significant orthostatic hypotension in early clinical pharmacology trials with normal human volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. APO-MIRTAZAPINE should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication).

Renal and hepatic impairment: Increased plasma concentrations of mirtazapine occur in patients with moderate and severe renal impairment and to a lesser extent in patients with hepatic impairment (See CLINICAL PHARMACOLOGY: Pharmacokinetic). In such patients, upward dose titration should be carefully monitored (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m^2 basis in mice and rats, respectively There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been enough to fully characterize the carcinogenic potential of mirtazapine tablets.

Mutagenesis: Mirtazapine was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, *in vitro* gene mutation assay in Chinese hamster V 79 cells, *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes, *in vivo* bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility: In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

Use in Pregnancy and Lactation

Safe use of APO-MIRTAZAPINE during pregnancy and lactation has not been established. Therefore, it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweighs the possible hazards to the child or fetus.

Post-marketing reports indicate that some neonates exposed to SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer anti-depressants, such as mirtazapine, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. The frequency of symptoms may vary with each drug. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants, or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS AND PRECAUTIONS-MAO Inhibitors). When treating a pregnant woman with APO-MIRTAZAPINE during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. (see DOSAGE AND ADMINISTRATION).

Pediatric Use
Safety and effectiveness in children under 18 years of age have not been established.

Geriatric Use
Pharmacokinetic studies revealed a decreased clearance in the elderly, especially elderly females. Elderly patients may be more susceptible to adverse events such as sedation, dizziness or confusion. Care should be exercised in dosage and titration to higher doses. [See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS (Somnolence)].

ADVERSE REACTIONS

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

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

All randomized placebo-controlled trials in patients (including indications other than major depressive disorder), have been evaluated for adverse reactions of mirtazapine. The meta-analysis considered 20 trials, with a planned duration of treatment up to 12 weeks, with 1501 patients (134 person years) receiving doses of mirtazapine up to 60 mg and 850 patients (79 person years) receiving placebo. Extension phases of these trials have been excluded to maintain comparability to placebo treatment.

Table 1 shows the categorized incidence of the adverse reactions, which occurred in the clinical trials statistically significantly more frequently during treatment with mirtazapine than with placebo, added with adverse reactions from spontaneous reporting. The frequencies of the adverse reactions from spontaneous reporting are based on the reporting rate of these events in the clinical trials. The frequency of adverse reactions from spontaneous reporting for which no

cases in the randomized placebo-controlled patient trials were observed with mirtazapine has been classified as 'not known'.

System organ class	Very common (≥1/10)	Common (≥1/100 to ≤1/10)	Uncommon (≥1/1,000 to ≤1/100)	Rare (≥1/10,000 to ≤1/1,000)	Frequency not known
Investigations	•Weight increased[1]				
Blood and the lymphatic system disorders					•Bone marrow depression (granulocytopenia, aggranulocytosis, aplastic anemia and thrombocytopenia) •Eosinophilia
Nervous system disorders	•Somnolence[1,4] •Sedation[1,4] •Headache[2]	•Lethargy[1] •Dizziness •Tremor	•Paraesthesia[2] •Restless legs •Syncope	• Myoclonus	
Gastrointestinal disorders	•Dry mouth	•Nausea[3] •Diarrhea[2] •Vomiting[2]	•Oral hypoaesthesia		•Mouth oedema
Skin and subcutaneous tissue disorders		•Exanthema[2]			
Musculoskeletal connective tissue and bone disorders		•Arthralgia •Myalgia •Back pain[1]			
Endocrine disorders					•Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	•Increase in appetite[1]				•Hyponatraemia
Vascular disorders		•Orthostatic hypotension	•Hypotension[2]		
General disorders and administration site conditions		•Oedema peripheral[1] •Fatigue			•Drug reaction with eosinophilia and systemic symptoms (DRESS)
Hepato-biliary disorders				•Elevation in serum transaminase activities	
Psychiatric disorders		•Abnormal dreams •Confusion •Anxiety[2,5] •Insomnia[3,5] •Amnesia	•Nightmares[2] •Mania •Agitation[2] •Hallucinations •Psychomotor restlessness (incl. akathisia, hyperkinesia)		•Suicidal ideation[6] •Suicidal behaviour[6]

[1] In clinical trials these events occurred statistically significantly more frequently during treatment with mirtazapine than with placebo.
[2] In clinical trials these events occurred more frequently during treatment with placebo than with mirtazapine, however not statistically significantly more frequently.
[3] In clinical trials these events occurred statistically significantly more frequently during treatment with placebo than mirtazapine.
[4] N.B. dose reduction generally does not lead to less somnolence/sedation but can jeopardize antidepressant efficacy.
[5] Upon treatment with antidepressants in general, anxiety and insomnia (which may be symptoms of depression) can develop or become aggravated. Under mirtazapine treatment, development or aggravation of anxiety and insomnia has been reported.
[6] Cases of suicidal ideation and suicidal behaviours have been reported during mirtazapine therapy or early after treatment discontinuation.

Adverse Reactions following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of mirtazapine (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

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.

  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. Caution should be advised and a closer clinical monitoring is required when these active substances arecombined with mirtazapine.

- Mirtazapine may increase the sedating properties of benzodiazepines and other sedatives (notably most antipsychotics, 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 cannot be excluded. it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Pharmacokinetic interactions

- Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine clearance about twofold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.

- Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine by approximately 40% and 50% respectively.

- When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with mirtazapine, the mean plasma concentration ofmirtazapine may increase more than 50 %. Caution should be exercised and the dose may have to be decreased when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.

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

DOSAGE AND ADMINISTRATION

APO-MIRTAZAPINE (mirtazapine) is not indicated for use in children under the 18 years of age (see WARNINGS AND PRECAUTIONS: Potential Association With Behavioural And Emotional Changes, Including Self-Harm)

ADULTS:

APO-MIRTAZAPINE Tablets should be administered as a single dose preferably in the evening prior to sleep. The recommended initial dose is 15 mg daily. In clinical trials, patients generally received doses of mirtazapine in the range of 15-45 mg/day. While a relationship between dose and antidepressant response for APO-MIRTAZAPINE has not been established, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day. (See ACTIONS AND CLINICAL PHARMACOLOGY, Clinical Trials Showing Efficacy sub-section). Mirtazapine has an elimination half-life of approximately 20-40 hours, therefore, dose changes should occur in intervals of not less than one week. Dosage adjustments may be made according to the tolerance and based on the patient's response.

Treatment should preferably be continued until the patient has been completely symptom-free for 4–6 months. After this, treatment can be gradually discontinued. Mirtazapine begins to exert its effect in general after 1–2 weeks of treatment.
Treatment with an adequate dose should result in a positive response within 2–4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2–4 weeks, then treatment should be stopped.

Discontinuation of APO-MIRTAZAPINE Treatment:

Symptoms associated with the discontinuation or dosage reduction of mirtazpine have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (See WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

A gradual reduction in the dose over several weeks rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER:

Post-marketing reports indicate that some neonates exposed to SSRIs, or other newer anti-depressants, such as mirtazapine, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS AND PRECAUTIONS). When treating pregnant women with APO-MIRTAZAPINE during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering APO-MIRTAZAPINE in the third trimester.

CHILDREN:

(see WARNINGSAND PRECAUTIONS: POTENTIAL ASSOCIATION WITH Behavioural AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)

ELDERLY AND PATIENTS WITH MODERATE TO SEVERE RENAL OR HEPATIC IMPAIRMENT:

In elderly patients, and patients with moderate to severe renal or hepatic impairment, limited pharmacokinetic data (see Pharmacology) demonstrates increased serum concentration and/or reduced clearance of mirtazapine. APO-MIRTAZAPINE should thus be dosed with care in these populations (See Pharmacokinetics Subsection of CLINICAL PHARMACOLOGY).

OVERDOSAGE

Human Experience: In clinical trials, the only drug overdose death reported while taking mirtazapine tablets was in combination with amitriptyline and chlorprohixene in a non-U.S. clinical study. Based on plasma levels, the mirtazapine dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. In other premarketing overdose cases with mirtazapine the following signs and symptoms were reported: disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with mirtazapine alone.

Overdose Management: Treatment should consist of those general measures employed in the management of overdose with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion or exchange transfusion in the treatment of mirtazapine overdosage. No specific antidotes for mirtazapine are known.

In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mirtazapine has a tetracyclic structure unrelated to selective serotonin reuptake inhibitors, tricyclic, or monoamine oxidase inhibitors. Mirtazapine enhances noradrenergic and specific serotonergic transmission.

Pharmacodynamics

Mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors which result in an increase in central noradrenergic and serotonergic activity. This action may explain its antidepressant activity.

Mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. The 5-HT_2 and 5-HT_3 antagonism by mirtazapine may account for its low rate of nausea, insomnia and anxiety as observed in clinical trials. Mirtazapine has no significant effect on 5-HT_{1A} and 5-HT_{1B} receptor.

Both enantiomers of mirtazapine appear to contribute to its pharmacological activity. The (+) enantiomer blocks 5-HT_2 receptors as well as α_2 receptors and the (-) enantiomer blocks 5-HT_3 receptors.

Mirtazapine is a potent histamine(H_1) receptor antagonist which may contribute to its sedative effect and possibly to weight gain due to increased appetite.

Mirtazapine is a moderate peripheral α_1 adrenergic antagonist, a property which may explain the occasional orthostatic hypotension reported in association with its use.

Mirtazapine is a moderate antagonist at muscarinic receptors, a property that may explain the occasional occurrence of anticholinergic side effects associated with its use as shown in clinical trials.

Pharmacokinetics

Mirtazapine is well-absorbed following oral administration and its absolute bioavailability is approximately 50% after either single or multiple doses. Peak plasma concentrations are reached within about 2 hours following an oral dose. The time to peak plasma concentration is independent of dose. The presence of food in the stomach somewhat slows the rate but not the extent of absorption, and thus does not require a dosage adjustment.

Plasma levels are linear over a dose range of 30 to 80 mg. Steady state plasma levels are attained within about 5 days. The half-life of elimination of mirtazapine after oral administration is approximately 20-40 hours.

Metabolism: Mirtazapine is extensively metabolized and quantitatively eliminated via urine (75%) and feces (15%); approximately 90% of this elimination occurs within the first 72-96 hours. Major pathways of biotransformation are demethylation and oxidation followed by conjugation. *In vitro* data from human liver microsomes indicate that cytochrome 2D6 and 1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas cytochrome 3A is considered to be responsible for the formation of the N-desmethyl and N-oxide metabolite. The demethyl metabolite is pharmacologically active and appears to have a similar pharmacokinetic profile as that of the parent compound.

The (-) enantiomer has an elimination half-life that is approximately twice as long, and achieves plasma levels that are three times as high as that of the (+) enantiomer.

Protein Binding: Mirtazapine is approximately 85% bound to plasma proteins over a concentration range of 10 to 1000 ng/mL. Binding appears to be both nonspecific and reversible. The binding affinity of mirtazapine to human liver proteins is 2.8 times greater than to human plasma proteins. As with all drugs that are protein bound, care should be exercised when co-administering medications that may interact with APO-MIRTAZAPINE at protein binding sites (See WARNINGS AND PRECAUTIONS).

Age and Sex: Following administration of mirtazapine 20 mg/day for 7 days, females of all-ages (range 25-74) exhibited significantly longer elimination half-lives than males (mean half-life 37 hours for females vs 26 hours for males) (see Table 2). Although these differences result on average in higher area-under-the-curve (AUC) for females compared to males, there is considerable overlap in individual AUCs between groups. Because of substantial individual variation of AUC and half-life, no specific dosage recommendations based on sex are indicated (see DOSAGE AND ADMINISTRATION).

In this same study oral clearance was reduced in older subjects (mean age 65; range 55-75) compared to younger subjects. The difference was greatest in males, with a 40% lower clearance for mirtazapine in the older vs younger group. Caution is indicated in administering APO-MIRTAZAPINE in the elderly (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

TABLE 2 Effect of Age and Gender on plasma half-life of mirtazapine t½ (mean ± SD)*

Group	Single Dose	Multiple Dose
Adult male N=9	21.7 ± 4.2	22.1 ± 3.7
Adult female N=9	37.7 ± 13.3	35.4 ± 13.7
Elderly# male N=8	32.2 ± 15.4	31.1 ± 15.1
Elderly# female N=8	40.6 ± 12.8	39.0 ± 10.8

* expressed in hours.

\# The 'elderly' group consisted of subjects 55 and older (55-75; mean age 65)

Liver Disease: In a single dose study conducted with mirtazapine 15 mg, the elimination half-life of mirtazapine was increased 40% in mild to moderately hepatically impaired subjects as compared to patients with normal hepatic function; this effect on elimination resulted in a 57% increase in AUC and a 33% decrease in clearance.

Renal Disease: In a single dose study conducted with mirtazapine 15 mg, subjects with moderate and severe renal impairment showed a significant decrease in the clearance of ORG 3770 and a consequent increase in the AUC (54% and 215% for moderate and severe renal impairment, respectively). Subjects with severe renal impairment had significantly higher peak plasma levels of ORG 3770 (about double that of subjects without renal impairment). These results suggest that caution must be exercised in administering APO-MIRTAZAPINE to patients who may have compromised renal function.

STORAGE AND STABILITY

Store below 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

In addition to the active ingredient, mirtazapine, each film coated tablet also contains lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide, red iron oxide (30 mg tablets) and yellow iron oxide (15 mg and 30 mg tablets).

APO-MIRTAZAPINE (mirtazapine) 15 mg Tablets: Pale yellow, oval shaped, scored, film coated tablets, engraved "APO" on one side and "MI" bisect "15" on the other side. Available in bottles of 30 tablets.

APO-MIRTAZAPINE (mirtazapine) 30 mg Tablets: Light pink, oval shaped, scored, film coated tablets, engraved "APO" on one side and "MI" bisect "30" on the other side. Available in bottles of 100 tablets.

APO-MIRTAZAPINE (mirtazapine) 45 mg Tablets: White to off-white, oval shaped, unscored, film coated tablets, engraved "APO" on one side and "MI-45" on the other side. Available in bottles of 30 and 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

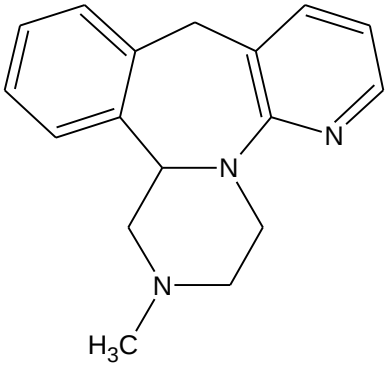
Proper Name: Mirtazapine

Chemical Name: Pyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, hemihydrate

1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3,-*c*]benzazepine, hemihydrate

Molecular formula and molecular weight: $C_{17}H_{19}N_3 \bullet 1/2\ H_2O$, 274.36

Structural Formula:



$\bullet 1/2\ H_2O$

Physicochemical properties: Mirtazapine is a white to yellowish white crystalline powder, which is practically insoluble in water, pKa of 7.1, pH of 7.54 (1% solution in water), melting point of 114 – 116°C (crystals from petroleum ether) and UV maximum absorption at 294 nm

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized single dose crossover comparative bioavailability study was performed on twenty-six (26) adult male and female volunteers (age range = 18 – 45 years) under fasting conditions. The rate and extent of absorption of mirtazapine was measured and compared following a single oral dose of 30 mg APO-MIRTAZAPINE (mirtazapine) or REMERON®, 30 mg tablets. The results from measured data are summarized in the following table.

Summary Table of the Comparative Bioavailability Data
Mirtazapine
(A Single 30 mg Dose: 1 x 30 mg)
From Measured Data
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test Apo-Mirtazapine	Reference Remeron®†	Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
AUC_{0-72} (pg•h/mL)	747362.49 789685.03 (34)	754494.15 788647.80 (29)	99.05	94.13 – 104.23
AUC_I (pg•h/mL)	814724.59 870303.70 (38)	826778.40 873896.19 (33)	98.54	93.4 – 103.97
C_{MAX} (pg/mL)	77951.51 82777.31 (34)	75937.43 79901.50 (32)	102.65	94.27 – 111.78
T_{MAX}* (h)	1.65 (46)	1.87 (47)		
$T_{½}$* (h)	23.02 (29)	23.68 (31)		

*Expressed as arithmetic means (CV%) only.

**Based on the least square means.

†Remeron® (manufactured by Organon Canada Ltd.) was purchased in Canada.

DETAILED PHARMACOLOGY

Mirtazapine and its enantiomers have been studied for their pharmacological effects in behavioral models for depression (Table 3) in mice and rats and in EEG-derived rat sleep-waking analysis and in receptor interaction studies (receptors for noradrenaline, serotonin (5-HT), histamine, acetylcholine and dopamine in rats and guinea-pigs).

Table 3: CNS-pharmacological profile of mirtazapine and its enantiomers

CNS-Pharmacological Profile	Mirtazapine	(S)+enant.	(R)-enant.
Behavioral models			
Antidepressant-like effects			
– bulbectomized rat: behavioral	+	+	-
– biochemical	+	-	+
– acquired immobility test	-	-	+
Anti-anxiety effects			
– anxiosoif test	±	±	±
EEG-studies			
Antidepressant profile			
– sleep (rat)	+	+	±
– sleep (human)	+	+	+
Receptor interactions			
Noradrenaline (α_2-blockade)			
– enhancement NA release	+	+	-
– rauwolscine displacement	+	+	-
– antagonism clonidine mydriasis	+	+	-
Serotonin			
– affinity $5HT_2$	+	+	±
– affinity $5HT_3$	+	-	+
Histamine			
– H_1-antagonism	+	+	+
Acetylcho line			
– QNB binding	-	-	-
– guinea-pig ileum	-	-	-

Pharmacological indices of side-effects/(Table 3)
The commonly observed side-effects of antidepressants that can be ascribed to receptor interactions are those of anticholinergic (dry mouth, blurred vision, constipation, urinary retention), α_1-adrenolytic (orthostatic hypotension) and antihistaminic (sedation) origin. Mirtazapine is virtually devoid of anticholinergic activity, as has been shown in *in-vitro* receptor interactions and confirmed in the *in-vivo* tremorine antagonism test. It is therefore predicted that the incidence of anticholinergic side-effects observed with mirtazapine in clinical practice should be low. This has been confirmed in clinical trials.

Mirtazapine is a moderately weak antagonist at central and peripheral α_1 adrenoceptors, as observed *in vitro* in the labelled prazosin binding assay in rat brain cortex homogenates and in the isolated rat vas deferens assay. On the basis of these observations a low incidence of orthostatic hypotension would be predicted, which is in line with the clinical observations in depressed patients.

Contribution of mirtazapine enantiomers to its pharmacological profile (Table 3)
In the acquired immobility test for antidepressant activity, both mirtazapine and the (S)+enantiomer are inactive, whereas the (R)-enantiomer is active.

In the olfactory bulbectomized rat subchronic treatment with the (S)+enantiomer reverses deficient behavior, whereas the (R)-enantiomer is inactive. However, the bulbectomy-induced decreases in noradrenaline and MHPG levels are reversed by subchronic treatment with the (R)-enantiomer, but not with the (S)+enantiomer.

Both enantiomers are active in the conflict-punishment test (display anti-anxiety activity) and in the sleep-waking EEG test in rats (suppression of REM sleep, an effect shared by many psychotropic drugs). In human pharmaco-EEG profiling in healthy volunteers [16] both enantiomers show a clearcut "antidepressant" profile, at similar dose-levels (0.5 and 1 mg per subject).

The enantiomers of mirtazapine differ considerably with respect to biochemical activity. The α_2-blocking activity of mirtazapine is virtually confined to the (S)+enantiomer, which is also the more potent $5HT_2$ antagonist. However, the (R)-enantiomer is the active principle in mirtazapine with regard to $5HT_3$ antagonistic activity. Both enantiomers contribute to a similar extent to the antihistaminic and (weak) α_1-adrenolytic properties of mirtazapine.

Contribution of mirtazapine main metabolites to its pharmacological profile
Demethyl Mirtazapine, the only metabolite found in the rat brain after oral administration of mirtazapine, has anti-anxiety activity in the conflict-punishment test in rats, but is less active in the rat EEG profile for antidepressant activity than the parent compound. The demethyl metabolite is also less active than the parent compound in *in-vivo* tests for α_2-blocking and $5HT_2$ antagonistic activity. This may be due to poor bioavailability upon systemic administration, since the *in vitro* tests show that the compound is approximately equally active to mirtazapine as an α_2 and $5HT_2$ antagonist, important indices for therapeutic antidepressant activity. With respect to antagonism at the histamine H_1 receptor, which is probably related to sedation, the demethyl metabolite appears to be less active than the parent compound.

8-hydroxy mirtazapine, 8-hydroxy demethyl mirtazapine and N(2)-oxide of mirtazapine have not been found to penetrate into the rat brain and are inactive *in vivo*, with the exception of the N(2)-oxide and the 8-hydroxy metabolite, which display some anti-serotonergic activity. *In vitro*, these metabolites are much less active than the parent compound at important receptors, like the α_2, $5HT_2$ and histamine H_1 receptors. They are, therefore, not considered to be relevant for the pharmacodynamic profile of mirtazapine, with regard to therapeutic activity or side-effects.

Glucuronide and sulphonate conjugates are not expected to be pharmacologically active and therefore only a limited number of *in vivo* and *in vitro* tests have been performed with these metabolites; they did not show any activity.

Cardiovascular pharmacology of mirtazapine

Cardiovascular effects
In conscious rabbits mirtazapine, at doses of 0.1 and 1.0 mg/kg i.v., has no effect on blood pressure, heart rate and the autonomic nervous system; at 10 mg/kg i.v., mirtazapine has also no effect on blood pressure and heart rate but slightly reduces the noradrenaline-induced increase in blood pressure and isoprenaline-induced increase in heart rate.

In anesthetized cats mirtazapine, at doses of 0.1 and 1.0 mg/kg i.v., induces no cardiovascular effects and does not affect the autonomic nervous system; at 10 mg/kg i.v., mirtazapine induces a decrease in blood pressure and heart rate and reduces the changes in blood pressure induced by vagus stimulation and carotid occlusion.

Hemodynamic effects
In anesthetized dogs mirtazapine, at 0.1 mg/kg i.v., does not induce any hemodynamic changes; at 1 .0 mg/kg i.v., mirtazapine slightly decreases heart rate and myocardial contractility and slightly increases peripheral vascular resistance; at 10 mg/kg i.v., mirtazapine induces a slight decrease in heart rate and stroke index resulting in a slightly decreased cardiac index, a decrease in myocardial contractility and an increase in peripheral vascular resistance resulting in decreased femoral and common carotid blood flow.

Cardiotoxicity
In artificially ventilated, anesthetized dogs cardiotoxicity has been investigated by infusing mirtazapine intravenously (30 mg/kg/h) until the animal died from cardiac arrest. If the animal was still alive 5 hours after the start of the infusion the experiment was stopped. Four out of five dogs died at the end of the 5-hour infusion period and one dog survived the infusion period. The mean extrapolated plasma level of mirtazapine prior to death in these four dogs was approximately 20 µg/mL; this is approximately 200 times the anticipated clinical peak plasma levels. There was a linear relationship between the severity of the cardiovascular effects (e.g. decrease in blood pressure, decrease in cardiac output and decrease in dP/dt) and the measured plasma level of mirtazapine.

TOXICOLOGY

Acute toxicity

The oral LD_{50}-value for mirtazapine in male Swiss mice was 830 mg/kg (760-940 mg/kg) after 24 hours and 810 mg/kg (720 - 1010 mg/kg) after 7 days and in females 720 mg/kg (620 - 850 mg/kg) after 24 hours and 7 days.

The oral LD_{50}-value for mirtazapine after 24 hours and 7 days was 490 mg/kg (427-534 mg/kg) and 320 mg/kg (240 - 430 mg/kg) in male and female Wistar rats respectively. In a separate study in rats, the enantiomers of mirtazapine displayed similar acute toxicity, the LD_{50} being 222 mg/kg and 208 mg/kg for the (R)- and (S)+enantiomers respectively.

Clinical signs observed in both species mainly at the highest doses included motor incoordination, reduced activity, ptosis, twitches, abnormally slow respiration and piloerection; these symptoms reached their peak 2 hours after administration and gradually disappeared during the first day. Gross anatomy revealed no drug-related morphological changes.

Repeated dose toxicity

Oral 13-week toxicity studies were carried out with mirtazapine in rats of both sexes followed by a 4-week recovery period with daily doses of 10,40 and 120 mg/kg, and in dogs of both sexes followed by a 7-week recovery period at daily doses of 5, 20, and 80 mg/kg. A second study in dogs was performed at a single dose level of 20 mg/kg/day to investigate possible changes in the prostate seen in the initial study in male dogs. One-year toxicity studies, followed by a five week recovery period, were carried out in rats and dogs with daily doses of 2.5, 20 and 120 mg/kg and 2.5, 15 and 80 mg/kg, respectively.

Subchronic toxicity

Oral administration of mirtazapine at 10 mg/kg/day to Wistar rats for 13 consecutive weeks induced no untoward effects, whereas mirtazapine at 40 and 120 mg/kg/day induced:

- transient clinical signs including mydriasis, lachrymation, ptosis, hypothermia, bradypnoea and hypersalivation (only females receiving 120 mg/kg)
- transient decrease in body weight gain and initial decrease in food consumption followed by an increase in food intake
- increased thyroidal weight (males only) associated with hypertrophy of thyroid follicular cells, a finding known to occur with compounds inducing microsomal hepatic enzymes in this species (see rat carcinogenicity study)
- increased adrenal gland weight (females only) not associated with morphological changes
- mild vacuolation of cortical renal tubules not associated with any other cytoplasmic or nuclear changes suggestive of degenerative/necrotic response, lipid deposition or any disturbances in renal function tests; this is not a nephrotoxic response as confirmed in the subsequent chronic toxicity study (see below)

- mild hepatic cell hypertrophy not indicative of hepatotoxicity and not accompanied by hepatic functional disturbances or degenerative changes

All these findings were reversible after a 4 week post-dosing period.

Oral administration of mirtazapine to Beagle dogs for 13 consecutive weeks induced:

- increased liver weights not associated with hepatoxicity at a dose level of 5, 20 and 80 mg/kg/day
- behavioral changes including incidental vomiting, loose defecation, reduced motor activity and body tremors at 20 and 80 mg/kg/day
- slight body weight loss in male dogs at 80 mg/kg/day
- decreased red blood cell parameters (hemoglobin and packed cell volume) at 80 mg/kg/day
- decreased testicular weight associated with reduced spermatogenesis, decreased epididymal weights and reduced epididymal spermatozoal content in two out of five animals at 80 mg/kg/day.

A significant decrease in prostatic weights was seen in all drug-treated animals as well as in a male in the control group kept for recovery. This effect was evaluated in a supplementary study (20 mg/kg/day for 13 consecutive weeks), after which it was concluded that the prostatic weight changes found in the first study most probably were not due to mirtazapine treatment but related to seasonal variations and age differences (younger males appearing to be more sensitive to changes in prostatic weight than the older animals). There is no evidence from the clinical studies to suggest that mirtazapine will affect the prostate in man.

Chronic toxicity

Oral administration of mirtazapine for one year to Sprague-Dawley rats (2.5, 20 and 120 mg/kg/day) and Beagle dogs (2.5, 15 and 80 mg/kg/day) did not induce any effects additional to those observed in the subchronic toxicity studies.

In the rat study, body weight in low-dose (males and females) and mid-dose (females) groups was generally slightly lower than in control animals; there was a marked decrease in body weight in the high-dose animals.

Microscopic examinations revealed that the only drug-related finding was an increased incidence of intracytoplasmic vacuolation in the renal proximal convoluted tubules in the high-dose group of rats after 6 months and those of the high and intermediate dose groups after 12 months. In addition there was an increased incidence of finely granular brown pigment in the cytoplasm of the tubular epithelial cells in the high-dose rats. The above-mentioned changes were not accompanied by any cytoplasmic or nuclear degenerative changes or by any disturbance in the renal function tests. From the light microscopy it was suggested that the vacuolations are the result of an increase in the size and numbers of the vacuoles constituting the endocytotic/lysosomal system in the proximal convoluted tubules. This was verified by electron microscopic examination of the kidneys. Vacuolations are known to occur whenever there is an incompatibility between material that enters the lysosomes and the digestive enzymes stored there. Thus in the chronic toxicity study with mirtazapine in rats, a transient incompatibility may have taken place due to overloading with the high dose of the test material. As in the subchronic thirteen-week study, tubular vacuolation and brown pigmentation were reversed during the one-month recovery period.

Oral administration of mirtazapine at 2.5 and 15 mg/kg/day to Beagle dogs for 12 months induced no untoward effects, whereas at 80 mg/kg/day induced:

- neurological signs (trembling and convulsions)
- decline in condition and mild gastro-intestinal disturbances
- body weight loss mainly during the first half of the dosing period
- decreases in red blood cell parameters (RBC, Hb, PCV)
- mild increases in alkaline phosphatase and glutamic-pyruvic transaminase during the first half of the dosing period together with liver enlargement and hepatic cell hypertrophy possibly indicative of enzyme induction. These changes were not associated with hepatic morphological changes indicative of hepatotoxicity after six or twelve months.
- increases in the erythroid/myeloid ratios in the bone marrow in males and to lesser extent females receiving 15 or 80 mg/kg/day after 52 weeks of dosing due to mildly decreased total myeloid elements in males and females and mildly increased erythroid elements in males.

Reversibility of the drug-related effects was seen after the one-month post-dosing period.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m^2 basis in mice and rats, respectively There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

The doses used in the mouse study may not have been enough to fully characterize the carcinogenic potential of mirtazapine Tablets.

Mutagenesis: Mirtazapine was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test, *in vitro* gene mutation assay in Chinese hamster V79 cells, *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes, *in vivo* bone marrow micronucleus test in rats, and unscheduled DNA synthesis assay in HeLa cells.

Impairment of Fertility: In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

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PART III: CONSUMER INFORMATION

PrAPO-MIRTAZAPINE
Mirtazapine Tablets

This leaflet is part III of a three-part "Product Monograph" published when APO-MIRTAZAPINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-MIRTAZAPINE. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

APO-MIRTAZAPINE is the generic brand name for a drug called mirtazapine.

What the medication is used for:
The most common use of APO-MIRTAZAPINE is for relief of depression symptoms.

What it does:
APO-MIRTAZAPINE is an antidepressant.

When it should not be used:
Do not use if allergic to mirtazapine or any of the nonmedicinal ingredients present in Apo-Mirtazapine (See "What the important non-medicinal ingredients are" section below). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.

What the medicinal ingredient is:
APO-MIRTAZAPINE tablets contain the active ingredient called mirtazapine.

What the important nonmedicinal ingredients are:
APO-MIRTAZAPINE tablets contain the following nonmedicinal ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol, titanium dioxide, yellow iron oxide (15 mg and 30 mg tablets only) and red iron oxide (30 mg tablets only).

What dosage forms it comes in:
Oral Tablets, 15 mg, 30 mg and 45 mg.

WARNINGS AND PRECAUTIONS

Before starting APO-MIRTAZAPINE and to get the best possible treatment, be sure to tell your doctor:

- all your medical conditions, including a history of seizures, liver or kidney disease, heart problems, diabetes, low blood pressure, glaucoma (increased intra-ocular pressure), high cholesterol and/or high triglycerides (fats in the blood) difficulties in urinating as a result of an enlarged prostate
- any medications (prescription or nonprescription) which you are taking, especially monoamine oxidase inhibitors (e.g. phenelzine sulphate, moclobemide, tranylcypromine sulphate, or selegeline), any other antidepressants, or drugs to treat anxiety
- any natural or herbal products you are taking (e.g. St. John's Wort)
- if you are pregnant or thinking of becoming pregnant, or if you are breast feeding
- your habits of alcohol consumption

- Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressants, such as APO-MIRTAZAPINE, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer anti-depressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the anti-depressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

- If you are pregnant and taking an SSRI or other newer anti-depressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Apo-Mirtazapine include monoamine oxidase inhibitors (e.g. phenelzine sulphate, moclobemide, tranylcypromine sulphate, or selegeline), any other antidepressants, drugs to treat anxiety, or any natural or herbal products (e.g. St. John's Wort).

Refrain from potentially hazardous tasks, such as driving a car or operating dangerous machines, until you are certain that this medication does not affect your mental alertness or physical coordination.

Avoid alcoholic drinks while taking APO-MIRTAZAPINE.

Before you use APO-MIRTAZAPINE talk to your doctor or pharmacist.

PROPER USE OF THIS MEDICATION

This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them, even if their symptoms are the same as yours.

Never increase or decrease the amount of APO-MIRTAZAPINE you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to and do not stop taking this medication without consulting your doctor.

Some symptoms may begin to improve within about two weeks but significant improvement can take several weeks. Continue to follow the doctor's instructions.

Usual dose:
The initial recommended dose is 15 mg/day. Dose may be increased up to 45 mg/day for unresponsive patients.

Tablets should be administered as a single evening dose (prior to sleep).

Do not chew. Do not use in pregnancy or nursing.

Overdose:
If you have taken a large number of pills all at once, immediately contact your doctor or the nearest hospital emergency department or your nearest Poison Control Centre, even though you may not feel sick. Show the doctor your pack of pills.

Missed Dose:
If you forget to take your evening dose, do not take the missed dose the next morning. Continue treatment in the evening (prior to sleep) with your normal dose. Do not take a double dose to make up for forgotten doses. Contact your doctor or pharmacist right away in case of doubt. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting sweating or other symptoms may occur after stopping or reducing the dosage of APO-MIRTAZAPINE.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.

You may experience some side effects such as increase in appetite, weight gain, drowsiness or sleepiness, swollen ankles or feet, occasional dizziness or faintness (especially when you get up quickly from a lying or sitting position) and headache. In rare cases other effects may include seizures, attack of mania, yellow colouring of eyes or skin, rash, abnormal sensation in the skin (e.g. burning, stinging, tickling or tingly) or restless legs. Some side effects are temporary. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

In very rare cases Apo-Mirtazapine may cause a shortage of white blood cells, resulting in a lowering of the body resistance to infection. If you have a fever, sore throat, mouth ulcers or any other signs of infection, you should immediately contact your doctor.

This is not a complete list of side effects. For any unexpected effects while taking APO-MIRTAZAPINE, contact your doctor or pharmacist.

HOW TO STORE IT

Remember to keep APO-MIRTAZAPINE well out of reach of children. APO-MIRTAZAPINE should be stored below 25°C.

For more information, please contact your doctor, pharmacist or other healthcare professional.

MORE INFORMATION

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