

PRODUCT MONOGRAPH

Pr AURO-MIRTAZAPINE OD

Mirtazapine Orally Disintegrating Tablets 15 mg, 30 mg and 45 mg
(House Standard)

Antidepressant

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Orally disintegrating tablets 15 mg, 30 mg and 45 mg	Crospovidone , mannitol, cellulose microcrystalline, aspartame (contains phenylalanine), colloidal anhydrous silica, magnesium stearate, strawberry flavor and peppermint flavor

INDICATIONS AND CLINICAL USE

Adults

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

Long-term use of Mirtazapine orally disintegrating tablets:

The efficacy of Mirtazapine orally disintegrating tablets 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. Nevertheless, the physician who elects to use AURO-MIRTAZAPINE OD for extended periods should periodically evaluate the long-term response of the individual patient to the drug.

Geriatrics (> 65 years of age):

Evidence from clinical trials and experience suggests that use in geriatric populations may be associated with differences in safety or effectiveness. A brief discussion can be found in the appropriate sections [see **WARNINGS AND PRECAUTIONS, Neurologic, Somnolence; Special Populations, Geriatrics (> 65 years of age); DOSAGE AND ADMINISTRATION; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**].

Pediatrics (< 18 years of age):

AURO-MIRTAZAPINE OD is not indicated for use in patients below the age of 18 years (see **WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm; see also ADVERSE REACTIONS/Pediatrics, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions/Pediatrics**).

CONTRAINDICATIONS

Hypersensitivity: AURO-MIRTAZAPINE OD is contraindicated in patients who are known to be hypersensitive to the drug or any of its components. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

Monoamine Oxidase Inhibitors:

In patients receiving agents that may affect the serotonergic neurotransmitter systems in combination with a monoamine oxidase (MAO) inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued (SSRI) Selective Serotonin Reuptake Inhibitor treatment and have begun treatment on a MAO inhibitor. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome (see **WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome**).

Therefore, AURO-MIRTAZAPINE OD should not be used in combination with MAO inhibitors (including the antibiotic linezolid, and the thiazine dye methylthionium blue (methylene blue), which are less well-known examples of MAO inhibitors) or within a minimum of 2 weeks of terminating treatment with MAO inhibitors. Treatment with AURO-MIRTAZAPINE OD should then be initiated cautiously and dosage increased gradually until optimal response is reached. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with AURO-MIRTAZAPINE OD.

WARNINGS AND PRECAUTIONS

General

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 (Selective Serotonin Reuptake Inhibitors) 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.**
- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

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, and 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 AURO-MIRTAZAPINE OD should NOT discontinue treatment 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.

Aspartame

AURO-MIRTAZAPINE OD contains aspartame, a source of phenylalanine, therefore, may be harmful for people with phenylketonuria.

Agranulocytosis

In pre-marketing clinical trials, two (one with Sjögren's Syndrome) out of 2,796 patients treated with Mirtazapine Tablets and one patient treated with imipramine developed agranulocytosis. In all three cases, the patients recovered after the drug with which they were being treated was stopped. In the post-marketing period with Mirtazapine Tablets, very rare cases of agranulocytosis have been reported, mostly reversible, but in some cases fatal. Fatal cases have mostly concerned patients above 65 years of age, although there has been at least one such fatality in a younger patient. Patients who are to receive Mirtazapine Orally Disintegrating Tablets should be warned about the risk of developing agranulocytosis, and advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with Mirtazapine Orally Disintegrating Tablets should be discontinued and the patient should be closely monitored.

Discontinuation of Treatment with AURO-MIRTAZAPINE OD

When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation, e.g. dizziness, abnormal dreams, sensory disturbances (including paresthesia 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**).

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis

See TOXICOLOGY for animal data.

Cardiovascular

QT Prolongation / Torsade de Pointes: Cases of QT prolongation, Torsades de Pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, 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 DRUG INTERACTIONS, Drug-Drug Interactions and OVERDOSAGE). Caution should be exercised when AURO-MIRTAZAPINE OD 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. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Cholesterol/Triglycerides: In U.S. short-term controlled studies, non-fasting cholesterol increases of >20% above the upper limits of normal were observed in 15% of patients taking Mirtazapine Tablets compared to 7% for placebo. In these same studies, non-fasting triglycerides increased to > 500 mg/dL in 6% of patients taking Mirtazapine Tablets compared to 3% for placebo.

Concomitant Illness

Use in Patients with Concomitant Illness: Clinical experience with mirtazapine in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing Mirtazapine Orally Disintegrating Tablets for patients with diseases or conditions that affect metabolism or hemodynamic responses.

Cardiovascular-Related History

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. Mirtazapine Orally Disintegrating Tablets 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).

Dependence/Tolerance

Physical and Psychological Dependence: Mirtazapine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of Mirtazapine Orally Disintegrating Tablets misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

Endocrine and Metabolism

Increased Appetite/Weight Gain: In U.S. short-term controlled studies the use of Mirtazapine Tablets was associated with increased appetite in 17% and the complaint of weight gain in 12 % of patients, compared to 2% for placebo in both cases. In these same trials, weight gain of $\geq 7\%$ occurred in 7.5% of the patients taking Mirtazapine Tablets compared to 0% in patients taking placebo. The average weight gain in the U.S. long-term controlled trials was 8 lbs. over 28 weeks.

Diabetes: Care should be taken in patients with diabetes mellitus. In patients with diabetes, antidepressants may alter glycaemia control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

Hyponatremia: Hyponatremia 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 hyponatremia.

Genitourinary

Although mirtazapine has very weak anticholinergic activity, care should be taken in patients with micturition disturbances like prostate hypertrophy.

Hematologic

Please refer to WARNINGS AND PRECAUTIONS, General, Agranulocytosis.

Hepatic/Biliary/Pancreatic

Hepatic Impairment: Increased plasma concentrations of mirtazapine occur in patients with moderate and severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). In such patients, upward dose titration should be carefully monitored (see **DOSAGE AND ADMINISTRATION**).

Transaminase Elevations: In U.S. short-term controlled studies, clinically significant ALT (SGPT) elevations (3 times the normal range) were noted in 2%, respectively, of patients treated with Mirtazapine Tablets and in 0% of patients treated with placebo. Most patients did not develop signs or symptoms associated with compromised liver function. While some patients discontinued treatment due to ALT increases, other patients with elevations continued with enzyme levels returning to normal during ongoing treatment. Mirtazapine should be used with caution in patients with impaired hepatic function (see **DOSAGE AND ADMINISTRATION**).

Jaundice: Treatment should be discontinued if jaundice occurs.

Neurologic

Somnolence: The use of Mirtazapine Tablets was associated with somnolence in 54% of patients in U.S. short-term controlled studies, compared to 18% with placebo. In these studies, somnolence resulted in 10% of mirtazapine-treated patients discontinuing treatment compared to 2% of placebo-treated patients. Mirtazapine Orally Disintegrating Tablets may cause mental or motor impairment because of this prominent sedative effect. Thus, patients should be cautioned about engaging in hazardous activities, such as driving a car or operating dangerous

machines, until they are reasonably certain that Mirtazapine Orally Disintegrating Tablets therapy does not adversely affect their ability to engage in such activities.

Akathisia/Psychomotor Restlessness

The use of antidepressants have been associated with the development of akathisia, characterized 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.

Dizziness: In U.S. short-term controlled studies, the use of Mirtazapine Tablets was associated with dizziness in 7% of patients, compared to 3% for placebo.

Activation of Mania/Hypomania: Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of Mirtazapine Tablets -treated patients in all U.S. studies (controlled and non-controlled). Although the incidence of mania/hypomania was very low during treatment with Mirtazapine Tablets, it should be used carefully in patients with a history of mania/hypomania.

Seizures: In pre-marketing clinical trials, only one seizure was reported in the 2,796 U.S. and non-U.S. patients treated with Mirtazapine Tablets. However, no controlled studies have been carried out in patients with a history of seizures. Therefore care should be exercised when AURO-MIRTAZAPINE OD is used in these patients.

Serotonin Syndrome/Neuroleptic Malignant Syndrome: On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment of Mirtazapine Orally Disintegrating Tablets, particularly when given in combination with other serotonergic and/or neuroleptic/antipsychotic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with Mirtazapine Orally Disintegrating Tablets should be discontinued if patients develop a combination of symptoms possibly including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome or neuroleptic malignant syndrome Mirtazapine Orally Disintegrating Tablets should not be used in combination with MAO inhibitors (including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs) or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in patients receiving other serotonergic drugs (triptans, lithium, tramadol, St. John's Wort, most tricyclic antidepressants) or neuroleptics/antipsychotics (**see CONTRAINDICATIONS and DRUG INTERACTIONS**).

Ophthalmologic

Care should be taken in patients with acute narrow-angle glaucoma and increased intra-ocular pressure.

Psychiatric

Suicide: Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As with any patient receiving anti-depressants, high-risk patients should be closely supervised during initial

drug therapy. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

In addition, a FDA meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Prescriptions of Mirtazapine Orally Disintegrating Tablets should be written for the smallest amount consistent with good patient management, in order to reduce the risk of overdose (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).

Renal

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 ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). In such patients, upward dose titration should be carefully monitored (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women: Safe use of Mirtazapine Orally Disintegrating Tablets during pregnancy 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 outweigh the possible hazards to the child or fetus.

Complications following late third trimester exposure to newer antidepressants:

Post-marketing reports indicate that some neonates exposed to SSRIs (Selective Serotonin Reuptake Inhibitors) or other newer anti-depressants, such as Mirtazapine Orally Disintegrating Tablets, 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, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome). When treating a pregnant woman with AURO-MIRTAZAPINE OD during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

The extent of exposure in pregnancy during clinical trials: None.

Nursing Women: Safe use of Mirtazapine Orally Disintegrating Tablets during lactation has not been established. Animal data and limited human data have detected mirtazapine in breast milk in low concentrations. A decision whether to continue/discontinue therapy with AURO-MIRTAZAPINE OD, or to continue/discontinue breast feeding should be made, taking into account the benefits and possible hazards to mother and infant.

Pediatrics (< 18 years of age): Safety and efficacy in children under 18 years of age have not been established. AURO-MIRTAZAPINE OD is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm; see also ADVERSE REACTIONS, Pediatrics; DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions/Pediatrics).

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Geriatrics (> 65 years of age): Pharmacokinetic studies revealed a decreased clearance in the elderly, with the lowest clearance in 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 ACTION AND CLINICAL PHARMACOLOGY; DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS, Neurologic, Somnolence).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse Events Leading to Discontinuation of Treatment:

Sixteen percent of patients treated with Mirtazapine Tablets in U.S. short-term controlled studies discontinued treatment due to an adverse event, compared to 7% of patients treated with placebo. The adverse event that accounted for more than 5% of discontinuations with Mirtazapine Tablets were somnolence (10%).

Commonly Observed Adverse Events in U.S. Short-Term Controlled Clinical Trials: The most commonly observed adverse events related to the use of Mirtazapine Tablets (5% or greater drug related incidence for mirtazapine tablets and at least twice that of placebo) were: somnolence (54% vs 18%), increased appetite (17% vs 2%), weight gain (12% vs 2%), dizziness (7% vs 3%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Events Occurring at an Incidence of 1% or More Among Mirtazapine Tablets-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more among Mirtazapine Tablets treated patients (and greater than the incidence in placebo-treated patients) who participated in U.S. short-term placebo-controlled trials, in which patients were dosed in a range of 5 to 60 mg/day. The investigators reported adverse clinical experiences using terms of their own choice. Reported adverse events were then classified using the standard COSTART-based dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1: Incidence of adverse clinical experiences (≥1% for Mirtazapine Tablets) IN U.S. short-term placebo-controlled studies ^{1,2,3}

Body System Adverse Event	Mirtazapine Tablets N = 453	Placebo N = 361
Body as a Whole		
Asthenia	34 (8%)	17 (5%)
Flu Syndrome	22 (5%)	9 (3%)
Back Pain	9 (2%)	3 (1%)
Digestive System		
Dry Mouth	112 (25%)	54 (15%)
Increased Appetite	76 (17%)	7 (2%)
Constipation	57 (13%)	24 (7%)
Metabolic and Nutritional Disorders		
Weight Gain	54 (12%)	6 (2%)
Peripheral Edema	11 (2%)	4 (1%)
Edema	6 (1%)	1 (0%)
Musculoskeletal System		
Myalgia	9 (2%)	3 (1%)
Nervous System		
Somnolence	243 (54%)	65 (18%)
Dizziness	33 (7%)	12 (3%)
Abnormal Dreams	19 (4%)	5 (1%)
Thinking Abnormal	15 (3%)	4 (1%)
Tremor	7 (2%)	2 (1%)
Confusion	9 (2%)	1 (0%)
Respiratory System		
Dyspnea	5 (1%)	1 (0%)
Urogenital System		
Urinary Frequency	8 (2%)	5 (1%)

- N = Number of Patients
- 1 % rounded off to the nearest whole integer
 - 2 Events which had an incidence on placebo > Mirtazapine Tablets: infection, pain, headache, nausea, diarrhea and insomnia.
 - 3 Events which had an incidence of Mirtazapine Tablets comparable to placebo: chest pain, palpitation, tachycardia, postural hypotension, dyspepsia, flatulence, libido decreased, hypertonia, nervousness, rhinitis, pharyngitis, sweating, amblyopia, tinnitus and taste perversion.

There was evidence of adaptation to some adverse events with continued therapy (e.g. increased appetite, dizziness and somnolence).

ECG Changes: The electrocardiograms for 338 patients who received Mirtazapine Tablets and 261 patients who received placebo in the U.S. short-term controlled trials were analyzed, in which the QTc calculations using the method of Fridericia was employed. Prolongation in QTc ≥ 500 msec was not observed among mirtazapine-treated patients. Mean change in QTc was +1.6 msec for mirtazapine and -3.1 msec for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm. for placebo. The clinical significance of these changes is unknown.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

During worldwide controlled and uncontrolled clinical trials, Mirtazapine Tablets were administered to 2,796 patients. The listing of events which follows includes those events which were judged by the investigator to be adverse clinical experiences. The investigators used terminology of their own choice to describe the adverse experiences. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized categories. It is important to emphasize that although the events occurred during treatment with Mirtazapine Tablets, they were not necessarily drug-related. Following the adverse experience tabulations, the incidence of clinically significant laboratory values which occurred at a rate of $\geq 1\%$ of patients is presented.

In the tabulations that follow, adverse events as reported by the investigator were classified using a standard COSTART-based Dictionary terminology. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1,000 patients; **rare** events are those occurring in fewer than 1/1,000 patients. Only those events not already listed in Table 1 appear in this listing. Events of major clinical importance are also described in the **WARNINGS AND PRECAUTIONS** section.

Body as a Whole: frequent: malaise, abdominal pain, abdominal syndrome acute; **infrequent:** chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; **rare:** cellulitis, substernal chest pain.

Cardiovascular System: frequent: hypertension, vasodilatation; **infrequent:** angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; **rare:** atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure.

Digestive System: **frequent:** vomiting, anorexia; **infrequent:** eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; **rare:** tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema.

Endocrine System: **rare:** goiter, hypothyroidism.

Hemic and Lymphatic Systems: **rare:** lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia.

Metabolic and Nutritional Disorders: **frequent:** thirst; **infrequent:** dehydration, weight loss; **rare:** gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus.

Musculoskeletal System: **frequent:** myasthenia, arthralgia; **infrequent:** arthritis, tenosynovitis; **rare:** pathologic fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis.

Nervous System: **frequent:** hypoesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; **infrequent:** aggression, ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; **rare:** aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome.

Respiratory Systems: **frequent:** cough increased, sinusitis; **infrequent:** epistaxis, bronchitis, asthma, pneumonia; **rare:** asphyxia, laryngitis, pneumothorax, hiccup.

Skin and Appendages: **frequent:** pruritus, rash; **infrequent:** acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; **rare:** urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer.

Special Senses: **infrequent:** eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; **rare:** blepharitis, partial transitory deafness, otitis media, taste loss, parosmia.

Urogenital System: **frequent:** urinary tract infection; **infrequent:** kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence, **rare:** polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency.

Pediatrics

The following adverse events were observed commonly in clinical trials in children: significant

weight gain ($\geq 7\%$) was observed in 48.8 % of the Mirtazapine Tablets treated subjects compared to 5.7 % in the placebo arm; urticaria (11.8 % vs. 6.8 %) and hypertriglyceridaemia (2.9 % vs. 0 %) were also commonly observed. (See also ACTION AND CLINICAL PHARMACOLOGY Special Populations and Conditions/Pediatrics).

Abnormal Hematologic and Clinical Chemistry Findings

Abnormal Laboratory Values: Elevated cholesterol, serum glucose and triglycerides were the most common blood chemistry parameters observed in U.S. studies.

The plasma samples were drawn from non-fasting patients, and these parameters are affected by diet. Patients taking Mirtazapine Tablets had increased appetite and weight gain, and are likely to have had increased food intake. Increased food intake may account for the increased triglyceride and cholesterol values. Moreover, LDL:HDL ratio data from a limited number of patients suggest that fat metabolism does not change with Mirtazapine Tablets treatment, further suggesting that the increase in triglyceride and cholesterol values reflected increased dietary intake.

Mild changes in liver function are shown by increases in liver enzymes. However, changes are temporary, mild, and are not expected to negatively influence liver function. Premature terminations due to liver enzyme abnormalities were, respectively, Mirtazapine Tablets, 1.7% and placebo, 1.1%.

The incidence of neutropenias in all clinical studies for Mirtazapine Tablets was 1.5%. Most of the observed cases of neutropenia were mild, isolated and nonprogressive (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

Adverse Events Observed During Post-Marketing Evaluation of Mirtazapine Tablets

Note: Adverse events reported during clinical trials, which were also reported during post-marketing, are not included in this section.

Adverse events reported since market introduction, which were temporally (but not necessary causally) related to mirtazapine therapy, include four cases of the ventricular arrhythmia torsades de pointes. In three of the four cases, however, concomitant drugs were implicated. All patients recovered.

Adverse events are listed under the appropriate System Organ Class

Blood and lymphatic system disorders: bone marrow depression (granulocytopenia, agranulocytopenia, aplastic anemia) (see also WARNINGS AND PRECAUTIONS, Agranulocytosis), eosinophilia.

Metabolism and nutrition disorders: hyponatremia.

Psychiatric disorders: insomnia, nightmares, psychomotor restlessness, suicidal ideation,

suicidal behaviours.

Nervous system disorders: headache, oral paresthesia, serotonin syndrome, restless legs, syncope, lethargy, sedation.

Investigations: electrocardiogram QT prolonged.

Cardiac disorders: cardiac arrest, long QT, torsade de pointes, sudden death, ventricular arrhythmia (torsade de pointes), ventricular fibrillation, ventricular tachycardia.

Vascular disorders: orthostatic hypotension

Gastrointestinal disorders: diarrhea, mouth edema, oral hypoaesthesia.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis.

General disorders and administration site conditions: Generalized and local edema, fatigue.

Adverse Reactions following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of Mirtazapine Tablets (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesia 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**).

Patients should be monitored for these or any other symptoms. 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 dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other anti-depressants with serotonergic effects (see **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

DRUG INTERACTIONS

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS**

Overview

As with other drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (see

ACTION AND CLINICAL PHARMACOLOGY).

The metabolism and pharmacokinetics of mirtazapine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Mirtazapine is extensively metabolized by CYP2D6, CYP3A4, and to a lesser extent by CYP1A2.

Drug-Drug Interactions

Monoamine Oxidase Inhibitors: Combined use of AURO-MIRTAZAPINE OD and monoamine oxidase inhibitors (**including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs**) is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Drugs Known to Prolong the QT Interval: 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.

Diazepam: The impairment of motor skills produced by mirtazapine has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking AURO-MIRTAZAPINE OD.

CYP Enzyme Inducers

CYP3A4 Inducers (these studies used both drugs at steady state):

- **Phenytoin:** In healthy male patients (n=18), phenytoin (200 mg daily) increased mirtazapine (30 mg daily) clearance, resulting in about a twofold decrease in plasma mirtazapine concentrations. Mirtazapine did not significantly affect the pharmacokinetics of phenytoin. During combined use of mirtazapine and phenytoin, 3 out of 19 patients experienced fatigue and 1 out of 19 patients developed rash (and none had experienced either fatigue or rash with mirtazapine alone or phenytoin alone). The rash was severe enough to necessitate withdrawal from the study.
- **Carbamazepine:** In healthy male patients (n=24), carbamazepine (400 mg b.i.d.) increased mirtazapine (15 mg b.i.d.) clearance, resulting in about a twofold decrease in plasma mirtazapine concentrations.

When phenytoin, carbamazepine or another inducer of hepatic metabolism (such as rifampicin) is added to mirtazapine therapy, the mirtazapine dose may have to be increased. If treatment with such a medicinal product is discontinued, it may be necessary to reduce the mirtazapine dose.

CYP Enzyme Inhibitors

Cimetidine: In healthy male patients (n=12), when cimetidine (800 mg b.i.d.) at steady state was co-administered with mirtazapine (30 mg daily) at steady state, the Area Under the Curve (AUC)

of mirtazapine increased by about 60%. Mirtazapine did not significantly change the pharmacokinetics of cimetidine. During combined use, side effects included somnolence [10 of 12 patients (including 1 of moderate severity) vs. 7 of 12 with mirtazapine alone and none with cimetidine alone], arrhythmia (2 of 12 patients vs. none with mirtazapine or cimetidine alone). The mirtazapine dose may have to be decreased when concomitant treatment with cimetidine is started, or increased when cimetidine treatment is discontinued.

Ketoconazole: In healthy, male, Caucasian patients (n=24), co-administration of the potent CYP3A4 inhibitor ketoconazole (200 mg b.i.d. for 6.5 days) increased the peak plasma levels and the AUC of a single 30 mg dose mirtazapine by approximately 40% and 50% respectively. During combined use, 2 severe adverse events have been reported: One patient experienced circulatory collapse and another patient experienced syncope. Both patients have lost consciousness for a brief period. Caution should be exercised when co-administering mirtazapine with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin or nefazodone.

Paroxetine: In an *in vivo* interaction study in healthy, CYP2D6 extensive metabolizer patients (n=24), mirtazapine (30 mg/day), at steady state, did not significantly change the pharmacokinetics of steady state paroxetine (40 mg/day), a CYP2D6 inhibitor. However, plasma concentrations of mirtazapine and its demethyl metabolite were slightly higher (about 18 and 25%, respectively) during combined administration with paroxetine. This difference is considered to be without clinical relevance. During combined use, side effects included exanthema (1 of 24 patients) that required withdrawal of the patient. Increases in AST and ALT were also reported, with a greater increase in men due to several outliers (including a patient that was withdrawn due to high AST (about 4 fold higher than the upper normal limit) and ALT (about 2 fold higher than the upper normal limit) levels; this patient also showed elevated WBC, neutrophils, decreased lymphocytes and basophils). AST/ALT levels returned to normal following the end of the treatment. Caution is advised for the co-administration of paroxetine with mirtazapine.

Other Drug-Drug Interactions

Amitriptyline: In healthy, CYP2D6 extensive metabolizer patients (n=32), amitriptyline (75 mg daily), at steady state, did not change the pharmacokinetics of steady state mirtazapine (30 mg daily) considerably and mirtazapine also did not change the pharmacokinetics of amitriptyline considerably. During combined use the following adverse reactions have been reported at considerably higher frequencies than with either drug alone: postural hypotension, impaired concentration (about 5 fold higher incidence), nausea (over 4 fold higher incidence) and dizziness (about 2 fold higher incidence). A CYP2D6 slow metabolizer patient experienced a serious adverse event following combined use of amitriptyline and mirtazapine. The subject complained of abdominal discomfort accompanied by dizziness and nausea and then leading to loss of consciousness for about 30 s. Apart from slight tremor (resembling myoclonic contractions) there were no other abnormalities. Caution is advised for the co-administration of amitriptyline with mirtazapine.

Warfarin: In healthy male subjects (n=16) mirtazapine (30 mg daily), at steady state, caused a small (0.2) but statistically significant increase in the International Normalised Ratio (INR) in subjects treated with warfarin to achieve subtherapeutic levels of prothrombin activity (1.5-2.0

INR) at steady state. As at a higher dose of mirtazapine, a more pronounced effect can not be excluded, it is advisable to monitor the INR in case of concomitant treatment of warfarin with mirtazapine.

Lithium: No relevant clinical effects or significant changes in pharmacokinetics have been observed in healthy male subjects on concurrent treatment with subtherapeutic levels of lithium (600 mg/day for 10 days) at steady state and a single 30 mg dose of mirtazapine. The serum levels of lithium were approximately 0.3 mmol/L 10 hrs after dosing. The effects of higher doses of lithium on the pharmacokinetics of mirtazapine are unknown.

Risperidone: In an *in vivo* non-randomized, interaction study subjects (n=6) in need of treatment with an antipsychiatric and antidepressant drug, the results of the effect of mirtazapine (30 mg daily) at steady state on the pharmacokinetics of risperidone (up to 3 mg b.i.d.) at steady state is inconclusive, due to high inter-patient variability and low number of patients. The study design does not permit conclusions to be made on the safety on the combined use of mirtazapine and risperidone. However, a case report of a male patient receiving combined treatment with mirtazapine (60 mg daily) and risperidone (3 mg daily) documents that, 6 weeks after initiation of this combination therapy, the patient developed pulmonary embolism and rhabdomyolysis. Caution is advised for the co-administration of risperidone with mirtazapine.

Serotonergic Drugs:

Based on the mechanism of action of mirtazapine and the potential for serotonin syndrome, caution is advised when AURO-MIRTAZAPINE OD is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, linezolid, methylene blue or St. John's Wort (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome**).

Drugs Bound to Plasma Protein: Because mirtazapine is bound to plasma proteins (85%), care should be exercised when AURO-MIRTAZAPINE OD is co-administered to a patient who may be receiving another drug which is highly protein-bound.

Drug-Herb Interactions

St. John's Wort: Pharmacodynamic interactions between mirtazapine orally disintegrating tablets and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects. Dose adjustment of AURO-MIRTAZAPINE OD should be considered if clinically indicated.

Drug-Lifestyle Interactions

Alcohol: The impairment of mental and motor skills produced by mirtazapine has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking AURO-MIRTAZAPINE OD.

DOSAGE AND ADMINISTRATION

AURO-MIRTAZAPINE OD is not indicated for use in children under 18 years of age (see WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

Mirtazapine Orally Disintegrating Tablets are unique tablets that are designed to rapidly disintegrate on the tongue. No water is needed to take the tablets.

Dosing Considerations

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER:

Post-marketing reports indicate that some neonates exposed to SSRI's or other newer anti-depressants, such as Mirtazapine Orally Disintegrating Tablets, 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 AURO-MIRTAZAPINE OD during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering AURO-MIRTAZAPINE OD in the third trimester.

Children:

See WARNINGS AND 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 ACTION AND CLINICAL PHARMACOLOGY) demonstrates increased serum concentration and/or reduced clearance of Mirtazapine Tablets. AURO-MIRTAZAPINE OD should thus be dosed with care in these populations (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Recommended Dose and Dosage Adjustment

INITIAL TREATMENT

ADULTS:

AURO-MIRTAZAPINE OD 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 Tablets in the range of 15 - 45 mg/day. While a relationship between dose and anti-depressant response for 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 ACTION AND CLINICAL PHARMACOLOGY, **Clinical Trials Showing Efficacy**). 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.

LONGER-TERM TREATMENT

It is generally agreed that acute episodes of depression require several months or longer of

sustained therapy beyond response to the acute episode. Systematic evaluation of mirtazapine has demonstrated that its efficacy in major depressive disorder is maintained for periods of up to 40 weeks following 8 - 12 weeks of initial treatment at a dose of 15 - 45 mg/day (see ACTION AND CLINICAL PHARMACOLOGY). Based on these limited data, it is unknown whether or not the dose of AURO-MIRTAZAPINE OD needed for continuation treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for continuation treatment and the appropriate dose for such treatment.

DISCONTINUATION OF AURO-MIRTAZAPINE OD TREATMENT

Symptoms associated with the discontinuation or dose reduction of AURO-MIRTAZAPINE OD have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction of AURO-MIRTAZAPINE OD (see **WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS**).

A gradual reduction in the dose over several weeks, rather than abrupt cessation, is recommended whenever is 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**).

Missed Dose

Do not take a double dose to make up for forgotten doses.

If a patient forgets to take the evening dose, advise the patient not to take the missed dose the next morning. Continue treatment in the evening (prior to sleep) with the normal dose.

Administration

Administration of Mirtazapine Orally Disintegrating Tablets

Patients should be instructed to open the tablet blister pack with dry hands and place the tablet on the tongue. The tablet should be used immediately after removal from the blister; once removed, it cannot be stored. AURO-MIRTAZAPINE OD will disintegrate rapidly on the tongue and can be swallowed with saliva. No water is needed for taking the tablet. Patients should not attempt to split the tablets (see PART III - **CONSUMER INFORMATION**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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 tablet dose taken was 30-45 mg, while plasma levels of amitriptyline and chlorprohixene were found to be at toxic levels. In other pre-marketing overdose cases with Mirtazapine tablets, 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 Tablets alone.

In post-marketing experience with more than 35 million patients exposed to Mirtazapine Tablets (based on average treatment courses of 30 mg/day during 3 months), fatal cases of overdose with Mirtazapine tablets alone have been reported. In many cases details regarding the precise dose are lacking. Fatal acute overdoses with Mirtazapine tablets alone are documented at doses as low as approximately 440 mg, which is estimated from the post-mortem plasma levels, assuming linear pharmacokinetics. However, survival has also been reported with a single Mirtazapine Tablets overdose as high as 1,350 mg.

Present experience concerning overdose with Mirtazapine tablets alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses. In these cases QT prolongation and Torsade de Pointes have also been reported.

Overdose Management:

Treatment should consist of those general measures employed in the management of overdose with any anti-depressant.

Ensure an adequate airway, oxygenation and ventilation. Monitor vital signs and cardiac rhythm (ECG monitoring should be undertaken) . General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Activated charcoal or gastric lavage may be appropriate.

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 centre for additional information on the treatment of any overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of Mirtazapine Orally Disintegrating Tablets, as with other drugs effective in the treatment of major depressive disorder, is unknown.

Evidence gathered in preclinical studies suggests that mirtazapine enhances central noradrenergic and serotonergic activity. These studies have shown that mirtazapine acts as an antagonist at central presynaptic α_2 -adrenergic inhibitory autoreceptors and heteroreceptors, an action that is postulated to result in an increase in central noradrenergic and serotonergic activity. The clinical relevance of this finding is unknown.

Pharmacodynamics

Mirtazapine acts as an antagonist at central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors, which results in an increase in central noradrenergic and serotonergic activity. The clinical relevance of this finding is unknown, however, this action may explain its anti-depressant activity.

Mirtazapine is a potent antagonist of 5-HT₂ and 5-HT₃ receptors. The clinical relevance of this finding is unclear, however, the 5-HT₂ and 5-HT₃ 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} receptors.

Both enantiomers of mirtazapine appear to contribute to its pharmacological activity. The (+) enantiomer blocks 5-HT₂ receptors as well as α_2 receptors, and the (-) enantiomer blocks 5-HT₃ receptors. The clinical relevance of this finding is unclear, but this may explain its anti-depressant activity and side-effect profile.

Mirtazapine is a potent histamine (H₁) 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.

Mirtazapine orally disintegrating tablets have been found bioequivalent to Mirtazapine Tablets.

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-demethyl 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 1,000 ng/mL. Binding appears to be both non-specific 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 mirtazapine at protein binding sites (see WARNINGS AND PRECAUTIONS).

Table 2: Effect of age and gender on plasma half-life of mirtazapine

Group	$T_{1/2}$ (mean \pm SD)*	
	Single Dose	Multiple Dose
Adult male N=9	21.7 \pm 4.2	22.1 \pm 3.7
Adult female N=9	37.7 \pm 13.3	35.4 \pm 13.7
Elderly# male N=8	32.2 \pm 15.4	31.1 \pm 15.1
Elderly# female N=8	40.6 \pm 12.8	39.0 \pm 10.8

* Expressed in hours

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

Special Populations and Conditions

Pediatrics: AURO-MIRTAZAPINE OD is not indicated for use in patients below the age of 18 years. Two randomised, double-blind, placebo-controlled trials in children aged between 7 and 18 years with major depressive disorder (n=259) failed to demonstrate significant differences between mirtazapine and placebo on the primary and all secondary endpoints. Significant weight gain ($\geq 7\%$) was observed in 48.8% of the mirtazapine treated subjects compared to 5.7% in the placebo arm. Urticaria (11.8% vs. 6.8%) and hypertriglyceridaemia (2.9% vs. 0%) were also commonly observed. (see **WARNINGS AND PRECAUTIONS-General Potential Association with Behavioural and Emotional Changes, Including Self-Harm; and DOSAGE AND ADMINISTRATION**).

Geriatrics: Following administration of mirtazapine 20 mg/day for 7 days, oral clearance was reduced in older subjects (mean age 65; range 55-75) compared to younger subjects (see Table 2). The difference was greatest in males, with a 40% lower clearance for mirtazapine in the older vs younger group, while clearance is lowest overall in elderly females. Caution is indicated in administering AURO-MIRTAZAPINE OD in the elderly (see **WARNINGS and PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Gender:

Age and Sex: In the same study above (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics) females of all ages (range 25 - 74) exhibited significantly longer elimination half-lives than males (mean half-life of 37 hours for females vs. 26 hours for males) (see Table 2). Although these differences result on average in higher 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).

Hepatic Insufficiency:

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 Insufficiency:

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 mirtazapine and a consequent increase in AUC (54% and 215% for moderate and severe renal impairment, respectively). Subjects with severe renal impairment had significantly higher peak plasma levels of mirtazapine (about double that of subjects without renal impairment). These results suggest that caution must be exercised in administering AURO-MIRTAZAPINE OD to patients who may have compromised renal function.

STORAGE AND STABILITY

Store at 15-30 °C. Protect from light and moisture. Use immediately upon opening individual tablet blister.

SPECIAL HANDLING INSTRUCTIONS

Patients should be instructed to open the tablet blister pack with dry hands and place the tablet on the tongue. The tablet should be used immediately after removal from the blister; once removed, it cannot be stored. AURO-MIRTAZAPINE OD will disintegrate rapidly on the tongue and can be swallowed with saliva. No water is needed for taking the tablet. Patients should not attempt to split the tablets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

15 mg tablets: Each white, round tablet debossed with '36' on one side and 'A' on the other side with an embossed circular edge contains 15mg mirtazapine for administration by the oral route. Nonmedicinal ingredients contained therein include crospovidone, mannitol, cellulose microcrystalline, aspartame (contains phenylalanine), colloidal anhydrous silica, magnesium stearate, strawberry flavor and peppermint flavor. They are available in blister packs of 6's. Five such blisters are available in one carton.

30 mg tablets: Each white, round tablet debossed with '37' on one side and 'A' on the other side with an embossed circular edge contains 30mg mirtazapine for administration by the oral route.

Nonmedicinal ingredients contained therein include crospovidone, mannitol, cellulose microcrystalline, aspartame (contains phenylalanine), colloidal anhydrous silica, magnesium stearate, strawberry flavor and peppermint flavor. They are available in blister packs of 6's. Five such blisters are available in one carton.

45 mg tablets: Each white, round tablet debossed with '38' on one side and 'A' on the other side with an embossed circular edge contains 45mg mirtazapine for administration by the oral route. Nonmedicinal ingredients contained therein include crospovidone, mannitol, cellulose microcrystalline, aspartame (contains phenylalanine), colloidal anhydrous silica, magnesium stearate, strawberry flavor and peppermint flavor. They are available in blister packs of 6's. Five such blisters are available in one carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

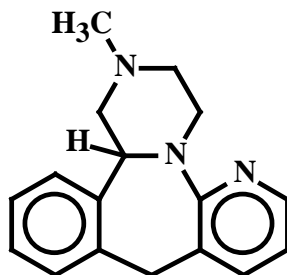
Drug Substance

Proper Name: Mirtazapine

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

Molecular Formula and molecular mass: C₁₇H₁₉N₃ and 265.36 g/mol

Structural Formula:



Physico-chemical properties:

Description	:	White to creamy white crystalline powder.
Melting Point	:	114° to 117°C
pH	:	7.89 (1%w/w dispersion)
pKa	:	7 (water at 25°C)
Solubility	:	Water (slightly soluble) 0.1N Hydrochloric acid (sparingly soluble) pH 4.5 acetate buffer (slightly soluble) pH 5.1 Acetate buffer (slightly soluble) pH 6.8 phosphate buffer (very slightly soluble)
Partition Coefficient	:	Log P (Octanol / Phosphate buffer pH 7.4) 3.09

CLINICAL TRIALS

Comparative Bioavailability Studies

An open label, randomized, two-treatment, two-sequence, two-period, cross-over, single dose comparative oral bioavailability study comparing test product, Mirtazapine Orally Disintegrating Tablets 45 mg and reference product Remeron RD 45 mg tablets, manufactured by Organon Canada Ltd., purchased from Canada was conducted in 24 healthy adult (in the age group of 18-40 years), male, human subjects under fasting conditions.

Table 3: Summary Table of Comparative Bioavailability Data

Analyte Name: Mirtazapine (1 x 45 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
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Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC ₀₋₇₂ (hr.ng/mL)	1445.98 1498.78(28.52)	1449.97 1501.13(27.27)	99.73	93.77-106.06
AUC _I (hr.ng/mL)	1658.15 1726.34(30.75)	1667.72 1732.12(30.08)	99.43	94.09-105.06
C _{max} (ng/mL)	108.43 111.30(22.61)	98.32 101.08(23.61)	110.28	100.45-121.07
T _{max} ‡ (h)	1.00(58.57)	1.67(54.79)		
T _{1/2} ‡ (h)	27.28(30.81)	27.41(32.89)		

* Mirtazapine orally disintegrating tablet manufactured by Aurobindo Pharma Ltd.

† Remeron RD manufactured by Organon Canada Ltd, was purchased in Canada

‡ Expressed as arithmetic mean (%CV) only

Clinical Trials Showing Efficacy

The efficacy of Mirtazapine Tablets in the treatment of depression was demonstrated in four US placebo-controlled trials (6 week duration) in adult outpatients meeting DSM III criteria for major depression. Patients were titrated with mirtazapine starting at a dose of 5 mg/day up to a dose of 35 mg/day (by the beginning of Week 3). Outcome measures included the Hamilton Depression Rating Scale (21-item) and the Montgomery and Asberg Depression Rating Scale. The mean mirtazapine dose for patients completing the four studies ranged from 21 to 32 mg/day. Additional supportive studies used higher doses up to 50 mg/day. In the U.S. short-term flexible-

- H ₁ -antagonism	+	+	+
Acetylcholine			
- QNB binding	-	-	-
- guinea pig ileum	-	-	-

Pharmacological Indices of Side-Effects (Table 4)

The commonly observed side-effects of anti-depressants 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 4)

In the acquired immobility test for anti-depressant 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 behaviour, 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 clear cut "anti-depressant" 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 5HT₂ antagonist. However, the (R)-enantiomer is the active principle in mirtazapine with regard to 5HT₃ 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 tablets, has anti-anxiety activity in the conflict-punishment test in rats, but is less active in the rat EEG profile for anti-depressant 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 5HT₂ 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 5HT₂ antagonist, important indices for therapeutic anti-depressant activity. With respect to antagonism at the histamine H₁ 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 , 5HT₂ and histamine H₁ 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 also has 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 0.1mg /kg *i.v.*, does not induce any hemodynamic changes; at 1.0mg/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 $\mu\text{g/mL}$; 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 LD₅₀ value for mirtazapine in male Swiss mice was 830 mg/kg (760 - 940 mg/kg) after 24 hours and 810 mg/kg (720-1,010 mg/kg) after 7 days, and in females, 720 mg/kg (620 – 850 mg/kg) after 24 hours and 7 days.

The oral LD₅₀ 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 LD₅₀ 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 hepatotoxicity at a dose levels of 5, 20 and 80 mg/kg/day
- behavioural 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 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. Based on AUC exposure, the highest doses used were approximately 0.7 and 1.2 times the maximum recommended human dose (MRHD) of 45 mg/day 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 tumours 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 Orally Disintegrating 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 (1.9 times the MRHD on an AUC basis). Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 1.3 times MRHD based on AUC, and pre-implantation losses occurred at 1.9 times MRHD based on AUC.

REFERENCES

1. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. *J Clin Psychiatry* 2000; 61:656-62.
2. Bremner JD, Smith WT. ORG 3770 vs. amitriptyline in the continuation treatment of depression: A placebo-controlled trial. *Eur J Psychiatr* 1996;10(1):5-15.
3. Dahl ML, Voortman G, Alm C, Elwin CE, Delbressine L, Vos R, et al. In vitro and in vivo studies on the disposition of mirtazapine in humans. *Clin Drug Invest* 1997; 13(Suppl 1):37-46.
4. de Boer T, Ruigt GSF. The selective α_2 -adrenoceptor antagonist mirtazapine (ORG 3770) enhances noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission. *CNS Drugs* 1995; 4(Suppl 1):29-38.
5. de Montigny C, Haddjeri N, Mongeau R, Blier P. The effects of mirtazapine on the interactions between central noradrenergic and serotonergic systems. *CNS Drugs* 1995;4(Suppl 1):13-7.
6. Holm KJ, Markham A. Mirtazapine: A review of its use in major depression. *Drugs* 1999; 57:607-31.
7. Leinonen E, Skarstein J, Behnke K, Agren H, Helsdingen JTH. Efficacy and tolerability of mirtazapine versus citalopram: A double-blind randomized study in patients with major depressive disorder. *Intl Clin Psychopharmacol* 1999; 14:329-37.
8. Leonard BE. Mechanisms of action of antidepressants. *CNS Drugs* 1995; 4(Suppl 1):1-12.
9. Loonen AJM, Doorschot CH, Oostelbos MCJM, Sitsen JMA. Lack of drug interactions between mirtazapine and risperidone in psychiatric patients: A pilot study. *Eur Neuropsychopharmacol* 1999; 10:51-7.
10. Montgomery SA. Safety of Mirtazapine: A review. *Int Clin Psychopharmacol* 1995; 10:37-45.
11. Peroutka SJ. Serotonin receptor subtypes: Their evolution and clinical relevance. *CNS Drugs* 1995; 4(Suppl 1):18-28.
12. Radhakishun FS, Bos JvdB, van der Heijden BCJM, Roes KCB, O'Hanlon JF. Mirtazapine Effects on alertness and sleep in patients as recorded by interactive telecommunication during treatment with different dosing regimens. *J Clin Psychopharmacol* 2000; 20:531-7.
13. Ruwe FJL, Smulders RA, Kleijn HJ, Hartmans HLA, Sitsen JMA. Mirtazapine and paroxetine: A drug-drug interaction study in healthy subjects. *Hum Psychopharmacol*

2001; 16:449-59.

14. Sennel C, Timmer CJ, Sitsen JMA. Mirtazapine in combination with amitriptyline: A drug-drug interaction study in healthy subjects. *Hum Psychopharmacol* 2003; 18(2):91-101.
15. Sitsen JMA, Maris FA, Timmer CJ. Concomitant use of mirtazapine and cimetidine: A drug-drug interaction study in healthy male subjects. *Eur J Clin Pharmacol* 2000; 56:389-94.
16. Sitsen JMA, Maris FA, Timmer CJ. Drug-drug interaction studies with mirtazapine and carbamazepine in healthy male subjects. *Eur J Drug Metab Pharmacokinet* 2001;26(1/2):109-21.
17. Sitsen JMA, Voortman G, Timmer CJ. Pharmacokinetics of mirtazapine and lithium in healthy male subjects. *J Psychopharmacol* 2000; 14:172-6.
18. Sitsen JMA and Zivkov M. Mirtazapine: Clinical profile. *CNS Drugs* 1995;4(Suppl 1):39-48.
19. Spaans E, van den Heuvel MW, Schnabel PG, Peeters PAM, Ching-kon-Sung UG, Colbers EPH, et al. Concomitant use of mirtazapine and phenytoin: A drug-drug interaction study in healthy male subjects. *Eur J Clin Pharmacol* 2002; 58:423-9.
20. Wheatly DP, van Moffaert M, Timmerman L, Kremer CME. Mirtazapine: Efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *J Clin Psychiatry* 1998; 59:306-12.
21. Product monograph of Remeron RD (Merck Canada Inc). Control # 168871. Date of Revision: January 15, 2014.

PART III: CONSUMER INFORMATION**Pr AURO-MIRTAZAPINE OD**

Mirtazapine Orally Disintegrating Tablets 15 mg, 30 mg
& 45 mg

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

ABOUT THIS MEDICATION**What the medication is used for:**

AURO-MIRTAZAPINE OD belongs to a group of medicines known as anti-depressants.

AURO-MIRTAZAPINE OD has been prescribed to you to relieve your symptoms of depression. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

What it does:

The way AURO-MIRTAZAPINE OD works to treat depression is unknown. AURO-MIRTAZAPINE OD is thought to have an effect in the brain on chemicals called serotonin and norepinephrine.

When it should not be used:

Do not use AURO-MIRTAZAPINE OD if you are:

- allergic to it or any of the components (see section What the important non-medicinal ingredients are);
- currently taking or have recently taken monoamine oxidase (MAO) inhibitors (including some types of anti-depressants and anti-Parkinson treatments) (see section INTERACTIONS WITH THIS MEDICATION).

What the important medicinal ingredient is:

Mirtazapine

What the nonmedicinal ingredients are:

Crospovidone, mannitol, cellulose microcrystalline, aspartame (contains phenylalanine), colloidal anhydrous silica, magnesium stearate, strawberry flavor and peppermint flavor.

What dosage forms it comes in:

Orally disintegrating tablets 15 mg, 30 mg and 45 mg

WARNINGS AND PRECAUTIONS

During treatment with these types of medications, it is important that you and your doctor have good ongoing communication about how you are feeling.

AURO-MIRTAZAPINE OD is not for use in children under 18 years of age.

New or Worsened Emotional or Behavioural Problems

Particularly in the first few weeks of treatment, 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; close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

BEFORE you use AURO-MIRTAZAPINE OD, talk to your doctor or pharmacist:

- if you have ever had an allergic reaction to any medication;
- if you have QT/QTc prolongation or a family history of QT/QTc prolongation;
- if you have heart disease;
- about all your medical conditions, including a history of seizures, liver or kidney disease, heart problems, such as certain kinds of heart conditions that may change your heart rhythm, a recent heart attack, heart failure, or take certain medicines that may affect the heart's rhythm, 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, psychiatric diseases such as schizophrenia and bipolar disorder (alternating periods of elation/overactivity and depressed mood);
- about any medications (prescription or non-prescription) which you are taking (refer to the next section for specific interactions with AURO-MIRTAZAPINE OD);
- about 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 breastfeeding;
- about your habits of alcohol consumption;
- if you have been told by your doctor that you have an intolerance to some sugars.

AURO-MIRTAZAPINE OD contains a source of phenylalanine. It may be harmful for people with phenylketonuria.

AURO-MIRTAZAPINE OD is not for use in children under 18 years of age.

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.

Contact your physician before stopping or reducing your dosage of AURO-MIRTAZAPINE OD. 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 AURO-MIRTAZAPINE OD. Such symptoms may

also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of AURO-MIRTAZAPINE OD to alleviate the symptoms.

Effects on Pregnancy and Newborns

If you are already taking/using AURO-MIRTAZAPINE OD and have just found out that you are pregnant, you should talk to your doctor immediately. You should also talk to your doctor if you are planning to become pregnant.

Possible complications at birth (from taking any newer antidepressant, including AURO-MIRTAZAPINE OD):

Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) or other newer anti-depressants, such as AURO-MIRTAZAPINE OD, 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, or nursing, and taking an SSRI or other newer anti-depressants, such as AURO-MIRTAZAPINE OD, 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. See also SIDE EFFECTS AND WHAT TO DO ABOUT THEM section.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

Do not use AURO-MIRTAZAPINE OD if you are taking or have recently taken:

- Monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine, moclobemide, selegiline, linezolid, methylene blue)
- Thioridazine
- Pimozide

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural/herbal), especially:

- other antidepressants, such as SSRIs, venlafaxine and certain tricyclics
- other drugs that affect serotonin such as tryptophan, triptans, lithium, tramadol, methylene blue (used to treat high levels of methemoglobin in the blood), St. John's Wort
- ketoconazole (medicine for treating fungal infections)
- cimetidine (used to treat reflux and stomach ulcers)

- erythromycin [used to treat bacterial infections (antibiotic)]
- drugs used to treat Human Immunodeficiency Virus (HIV), such as a combination of fosamprenavir and ritonavir
- nefazodone (used to treat depression)
- certain drugs used to treat epilepsy, such as carbamazepine and phenytoin
- rifampicin (used to treat tuberculosis),
- warfarin (used to prevent blood clotting),
- benzodiazepines (e.g., midazolam, oxazepam and diazepam) as AURO-MIRTAZAPINE OD may add to the sedative effects of these agents.
- medicines that may affect the heart's rhythm such as certain antibiotic and some anti-psychotics

Avoid alcoholic drinks while taking AURO-MIRTAZAPINE OD.

PROPER USE OF THIS MEDICATION

Usual dose:

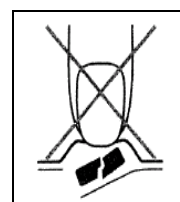
It is very important that you take AURO-MIRTAZAPINE OD exactly as your doctor has instructed. Generally, most people take between 15 mg and 45 mg per day.

How to take AURO-MIRTAZAPINE OD:

- Never increase or decrease the amount of AURO-MIRTAZAPINE OD 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. (see WARNINGS and PRECAUTIONS when taking AURO-MIRTAZAPINE OD).
- Some symptoms may begin to improve within about two weeks, but significant improvement can take several weeks. Continue to follow the doctor's instructions.
- The tablets should be taken at the same time each day, preferably as a single evening dose (prior to sleep). Do not chew them.
- Keep taking your tablets until the doctor tells you to stop. The doctor may tell you to take your medicine for several months. Continue to follow the doctor's instructions.
- 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.

The tablet(s) should be taken as follows:

- In order to prevent crushing the tablet, do not push against the tablet pocket (Figure A)



(FIGURE A)

- Each strip contains six tablet pockets, which are separated by perforations. Bend the strip as indicated. Tear off one tablet pocket along the dotted lines. (Figure 1)

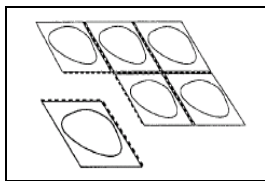


FIGURE 1

- Carefully peel off the lidding foil, starting in the corner indicated by the arrow (Figures 2 and 3)

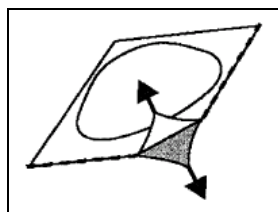


FIGURE 2

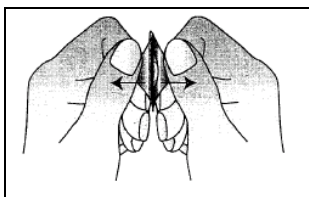


FIGURE 3

- Take out the tablet (making sure hands are dry) and place it on the tongue. (Figure 4). The tablet will rapidly disintegrate and can be swallowed without water

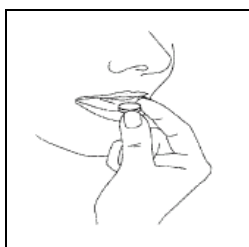


FIGURE 4

- The tablet should be used immediately after removal from its blister; once removed, it cannot be stored.
- Do not attempt to split the tablet.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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

The most likely signs of an overdose of AURO-MIRTAZAPINE OD (without other medicines or alcohol) are drowsiness, disorientation and increased heart rate. The symptoms of a possible overdose may include changes to your heart rhythm (fast, irregular heartbeat) and/or fainting which could be symptoms of a life-threatening condition known as Torsade de Pointes.

Missed Dose:

- Do not take a double dose to make up for forgotten doses. 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, AURO-MIRTAZAPINE OD can cause some side effects. You may not experience any of them. For most patients, side effects are likely to be minor and temporary. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

- You may experience some side effects, such as increase in appetite, swollen ankles or feet, occasional dizziness or faintness (especially when you get up quickly from a lying or sitting position), nausea, headache, localized swelling, swelling throughout the body and speech disorder.
- In rare cases, other effects may include rash, abnormal sensation in the skin (e.g., burning, stinging, tickling or tingly), involuntary trembling of muscles (tremor), dry mouth, tiredness.
- In very rare cases, other effects may include abnormal sensations in the mouth, sensations of numbness in the mouth and swelling in the mouth.

Some side effects are temporary. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

Decrease in White Blood Cells

If you experience signs of infection such as sudden unexplainable high fever, chills, sore throat and mouth or nose sores, tell your doctor right away. In rare cases, AURO-MIRTAZAPINE OD can cause a decrease in white blood cells, which are needed to fight infection.

New or Worsened Emotional or Behavioural Problems

A small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience new or worsened feelings of agitation, hostility or anxiety, or thoughts about suicide. Your doctor should be informed of such changes immediately. Close observation by a doctor is necessary in this situation. Do not discontinue your medication on your own. See also the WARNINGS AND PRECAUTIONS section.

Discontinuation Symptoms

Contact your doctor before stopping or reducing your dosage of AURO-MIRTAZAPINE OD. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting, sweating and other symptoms have been reported after stopping AURO-MIRTAZAPINE OD. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of AURO-MIRTAZAPINE OD to alleviate the symptoms. See WARNINGS AND PRECAUTIONS section for more information.

Effects on Newborns

Some newborns whose mothers took an SSRI or other newer antidepressants during pregnancy have shown such symptoms as breathing and feeding difficulties, jitteriness and constant crying. If your baby experiences any of these symptoms, contact your doctor as soon as you can. See WARNINGS AND PRECAUTIONS section for more information.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
	Only if severe	In all cases	
Jaundice (yellowing of eyes or skin; dark urine)			√
Symptoms of depression (anxiety and disturbed sleep)	√		
Severe skin reactions such as Stevens-Johnson syndrome (fever, rash, swollen lymph nodes, hives, sore mouth, sore eyes or swelling of lips or tongue)			√
Low sodium levels in blood (feeling ill with symptoms of weakness, drowsiness, confusion, combined with achy, stiff or uncoordinated muscles)			√
Abdominal pain and nausea; this may suggest inflammation of the pancreas (pancreatitis)	√		
Very Rare A combination of symptoms such as unexplainable fever, sweating, increased heart rate, diarrhea, (uncontrollable) muscle contractions, shivering, overactive reflexes, restlessness, mood changes and unconsciousness (can be signs of serotonin syndrome)			√
See WARNINGS & PRECAUTIONS New or worsened emotional or behavioural problems			√
Unknown Abnormal heart rate or rhythm, palpitations, fainting		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
	Only if severe	In all cases	
Common Drowsiness which can lead to impaired concentration. Generally occurring during the first few weeks of treatment Weight gain	√		
Infrequent Aggression			√
Rare Bruising and/or unusual bleeding and symptoms of infection such as sudden high fever, sore throat, mouth ulcers, severe digestive system disturbances or other signs of infection (symptoms of blood cell disturbances). Convulsions (loss of consciousness with uncontrollable shaking) Fainting/loss of consciousness Nightmares/vivid dreams, agitation or confusion. Hallucinations (strange visions or sounds) Mania (feeling elated or Emotionally 'high') Akathisia (feeling restless and unable to stand still) Uncontrolled, sudden movements Restless legs (feeling of unrest during night mainly located in the legs combined with sudden muscle contractions in the legs) Pain in the joints or muscles		√	
			√
			√
			√
		√	
		√	
		√	
			√

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

HOW TO STORE IT

- Store at 15-30 °C. Protect from light and moisture. Use immediately upon opening individual tablet blister.
- Keep AURO-MIRTAZAPINE OD out of the reach and sight of children.
- Do not use AURO-MIRTAZAPINE OD after the expiry date indicated on the package.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.auropharma.ca> or by contacting the sponsor, Auro Pharma Inc., at: 1-855-648-6681

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