PRODUCT MONOGRAPH

PrRHOXAL-MIRTAZAPINE FC

15 and 30 mg tablets

Antidepressant

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PrRHOXAL-MIRTAZAPINE FC

Mirtazapine

15 and 30 mg Tablets

Antidepressant

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

For symptomatic relief of depressive illness. The effectiveness of mirtazapine in long-term use (more than 6 weeks) has not been systematically evaluated in controlled clinical trials. Therefore, the physician who elects to use Rhoxal-mirtazapine FC for extended periods should periodically evaluate the long-term response of the individual patient to the drug.

CONTRAINDICATIONS

Rhoxal-mirtazapine FC tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS AND PRECAUTIONS

Agranulocytosis: In premarketing 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. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with Rhoxal-mirtazapine FC should be discontinued and the patient should be closely monitored.

MAO Inhibitors: In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, e.g., including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Since there are no human data studying such an interaction with mirtazapine, it is recommended that Rhoxal-mirtazapine FC not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

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 discontinuation of 10% of mirtazapine-treated patients compared to 2% of placebo-treated patients. Rhoxal-mirtazapine FC 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 Rhoxal-mirtazapine FC therapy does not adversely affect their ability to engage in such activities.

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

Increased Appetite/Weight Gain: In U.S. short-term controlled studies the use of mirtazapine 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 7% occurred in 7.5% of the patients taking mirtazapine compared to 0% in patients taking placebo. The average weight gain in the US long-term controlled trials was 8 lbs. over 28 weeks.

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 compared to 7% for placebo. In these same studies, non-fasting triglycerides increased to > 500 mg/dl in 6% of patients taking mirtazapine compared to 3% for placebo.

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 mirtazapineand in 0% of patients treated with placebo. Most patients did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued 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).

Activation of Mania/Hypomania: Mania/hypomania occurred in approximately 0.2% (3/1,299 patients) of mirtazapine treated patients in all U.S. studies (controlled and non-controlled).

Although the incidence of mania/hypomania was very low during treatment with mirtazapine, 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. However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when Rhoxal-mirtazapine FC is used in these patients.

Suicide: Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescription of Rhoxal-mirtazapine FC should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose.

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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. Adverse events that accounted for more than 5% of discontinuations with mirtazapine were somnolence (10%).

Commonly Observed Adverse Events in US Short-Term Controlled Clinical Trials: The most commonly observed adverse events related to the use of mirtazapine (5% or greater drug related incidence for mirtazapine 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%).

Adverse Events Occurring at an Incidence of 1% or More Among Mirtazapine Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more among mirtazapine 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 investigator 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 2
INCIDENCE OF ADVERSE CLINICAL EXPERIENCES (≥1% for MIRTAZAPINE)

IN U.S. Short-Term PLACEBO-CONTROLLED STUDIES[1,2,3]

Body System Adverse Clinical Experience N=Number of Patients	U.S. Studies	
	Mirtazapine 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%)

[1] % rounded off to the nearest whole integer

[2] Events which had an incidence on placebo > mirtazapine: infection, pain, headache, nausea, diarrhea and insomnia.

[3] Events which had an incidence of mirtazapine 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 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 $\geq$ 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.

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

The plasma samples were drawn from non-fasting patients, and these parameters are affected by diet. Patients taking mirtazapine 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 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 mirtazapine 1.7% and placebo 1.1%.

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

Other Adverse Events Observed During the Premarketing Evaluation of Mirtazapine: During worldwide controlled and uncontrolled clinical trials, mirtazapine was administered to 2,796 patients. The listing of events which follows are 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, they were not necessarily drug related. Following the adverse experiences tabulations, the incidence of clinically significant laboratory values which occurred at a rate of 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 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in Table 2 appear in this listing. Events of major clinical importance are also described in the WARNINGS & 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, chest pain substernal.

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 System:
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, arthosis, bursitis.

Nervous System:

Frequent: Hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia.
Infrequent: Ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidial 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 accomodation, 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.

Other Adverse Events Obeserved During Postmarketing Evaluation of Mirtazapine:
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 Reactions following Discontinuation of Treatment (or Dose Reduction):
There have been reports of adverse reactions upon the discontinuation of mirtazapine (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see WARNINGS & 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 the 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 antidepressants with serotonergic effects (see WARNINGS & PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DRUG INTERACTIONS

Drug-Drug Interactions

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 & CLINICAL PHARMACOLOGY).

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of mirtazapine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Drugs Metabolized by Cytochrome P4502D6: Many drugs are metabolized by and/or inhibit various cytochrome P450 isoenzymes eg., 2D6, 1A2, 3A4 etc. In vitro studies have shown that mirtazapine is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While in vitro studies have also shown that mirtazapine is not a potent inhibitor of any of these enzymes, the concomitant use of mirtazapine with other drugs metabolized by these enzymes has not been formally evaluated. Therefore, it is not possible to make any definite statements about the risks of coadministration of Rhoxal-mirtazapine FC with such drugs.

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

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

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 Rhoxal-mirtazapine FC.

Drug-Herb Interactions

St. John's Wort: In common with SSRI's and SNRI's, pharmacodynamic interactions between mirtazapine and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects. Dose adjustment of mirtazapine should be considered if clinically indicated.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults: Rhoxal-mirtazapine FC tablets should be administered as a single dose preferably in the evening prior to sleep. The recommended initial dose is 15 mg daily. In clinical trials, patients generally received doses of mirtazapine in the range of 15-45 mg/day. While a relationship between dose and antidepressant response for 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 & CLINICAL PHARMACOLOGY, Clinical Trials Showing Efficacy sub-section). Mirtazapine has an elimination half-life of approximately 20-40 hours, therefore, dose changes should occur in intervals of not less than one week.

Discontinuation of Rhoxal-mirtazapine FC treatment: Symptoms associated with the discontinuation or dosage reduction of Rhoxal-mirtazapine FC have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (See WARNINGS & PRECAUTIONS and ADVERSE REACTIONS).

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

Elderly and Patients with Moderate to Severe Renal or Hepatic Impairment: In elderly patients, and patients with moderate to severe renal or hepatic impairment, limited pharmacokinetic data (see Pharmacology) demonstrates increased serum concentration and/or reduced clearance of mirtazapine. Rhoxal-mirtazapine FC should thus be dosed with care in these populations (See Pharmacokinetics Subsection of ACTION & CLINICAL PHARMACOLOGY).

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 behavior, 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 Rhoxal-mirtazapine FC misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

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

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

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

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

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

ACTION AND CLINICAL PHARMACOLOGY

Rhoxal-mirtazapine FC has a tetracyclic structure unrelated to selective serotonin reuptake inhibitors, tricyclic, or monoamine oxidase inhibitors.

Rhoxal-mirtazapine FC enhances noradrenergic and specific serotonergic transmission.

Pharmacodynamics

Mirtazapine acts as an antagonist at central presynaptic α2 adrenergic inhibitory autoreceptors and heteroreceptors which result in an increase in central noradrenergic and serotonergic activity. This action may explain its antidepressant activity.

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

Both enantiomers of Rhoxal-mirtazapine FC appear to contribute to its pharmacological activity. The (+) enantiomer blocks 5-HT_2 receptors as well as α2 receptors and the (-) enantiomer blocks 5-HT_3 receptors.

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

Mirtazapine is a moderate peripheral α1 adrenergic antagonist, a property which may explain the occasional orthostatic hypotension reported in association with its use.

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

Pharmacokinetics

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

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

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

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

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

Age and Sex: Following administration of mirtazapine 20 mg/day for 7 days, females of all-ages (range 25-74) exhibited significantly longer elimination half-lives than males (mean half-life 37 hours for females vs 26 hours for males) (see Table 1). Although these differences result on average in higher area-under-the-curve (AUC) for female compared to males, there is considerable overlap in individual AUCs between groups. Because of substantial individual variation of AUC and half-life, no specific dosage recommendations based on sex are indicated (see DOSAGE and ADMINISTRATION).
In this same study, oral clearance was reduced in older subjects (mean age 65; range 55-75) compared to younger subjects. The difference was greatest in males, with a 40% lower clearance for mirtazapine in the older vs younger group. Caution is indicated in administering Rhoxal-mirtazapine FC in the elderly (see WARNINGS & PRECAUTIONS, and DOSAGE and ADMINISTRATION).

TABLE 1
Effect of Age and Gender on plasma half-life of mirtazapine
$t_{1/2}$ (mean ± SD)*

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

* expressed in hours.**The 'elderly' group consisted of subjects 55 and older (55-75; mean age 65)

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

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

Clinical Trials Showing Efficacy

The efficacy of mirtazapine 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-dose controlled trials (mirtazapine, N=323), 70% and 54% of the patients received final doses 20 mg and 25 mg, respectively.

STORAGE AND STABILITY

Store at room temperature, 15-30˚C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

15 mg tablets: Yellow, round, biconvex, beveled-edge, film coated tablet debossed "E" over "20" on one side and bisected on the other side, available in HDPE bottles of 30 and 100.
30 mg tablets: Red-brown, oval shaped, film-coated tablet, debossed "M30" on one side and bisected on the other side, available in HDPE bottles of 30 and 100.

Dispense in a tight, light resistant container.

Composition

15 mg tablets: Each film coated tablet of Rhoxal-mirtazapine FC contains 15 mg of active drug substance, mirtazapine. Non-medicinal ingredients include lactose monohydrate, colloidal silicon dioxide, pregelatinized starch, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, iron oxide yellow, polysorbate 80.

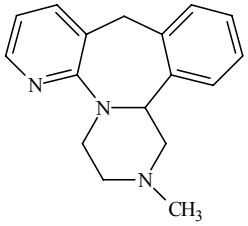
30 mg tablets: Each film coated tablet of Rhoxal-mirtazapine FC contains 30 mg of active drug substance, mirtazapine. Non-medicinal ingredients include lactose monohydrate, colloidal silicon dioxide, pregelatinized starch, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, FD & C yellow No. 6, polysorbate 80, iron oxide red.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Mirtazapine
Chemical Name: (±)-1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine
Structural Formula:



Molecular Formula: $C_{17}H_{19}N_3$
Molecular Weight: 265.36
pKa: 6.89
Melting range: 115-116 ˚C
Partition coefficient:

pH of buffer solution	Po/w (20°C)
2	0.0085
4	4.674
7	208.7
9	2143

Hygroscopicity:

Relative humidity	Hygroscopicity (%) (storage period)		
	3 days	**5 days**	**7 days**
63.5% (Ammonium nitrate)*	1.92	1.97	1.99
75% RH (Sodium chloride)*	1.89	1.95	1.97
93% RH (Potassium nitrate)*	2.12	2.45	2.42

* name of inorganic salt used to provide the saturated solutions.

Description: Mirtazapine is a white to creamy white crystalline powder which is practically insoluble in water. Mirtazapine was found to have the following solubility in buffer solutions at pH 2, pH 4, and pH 9:

pH (pH of saturated solution)	concentration (mg/mL)	solubility
2 (1.95)	3.53	Slightly soluble
4 (3.87)	4.66	Slightly soluble
9 (8.75)	0.072	Practically soluble

CLINICAL TRIALS

Comparative Bioavailability Study

Single dose crossover comparative bioavailability study of mirtazapine 30 mg tablets in healthy male volunteers (18 to 50 years old) was conducted under fasted conditions. Bioavailability data were measured and the results are summarized in the following table.

Mirtazapine (1 x 30 mg Tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test Rhoxal-mirtazapine FC tablets	Reference Remeron™ †	% Ratio of Geometric Means	90 % Confidence Interval
AUC_T (ng.h/mL)	597.24 621.05 (27.8)	594.18 617.78 (28.2)	100.51	96.10-105.13
AUC_I (ng.h/mL)	658.30 686.69 (28.9)	655.60 685.81 (30.7)	100.41	96.05-104.97
C_{MAX} (ng/mL)	60.52 63.27 (31.2)	58.51 61.58 (33.8)	103.42	94.93-112.68
T_{MAX}^{*} (h)	1.50 (1.00-3.33)	1.67 (1.00-3.67)	---	---
$T_{½}^{**}$ (h)	21.90 (30.4)	22.31 (29.2)	---	---

† Remeron™ is manufactured by Organon. Remeron™ was purchased in Canada.
* expressed as the median (range) only.
** expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

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

TABLE 3: CNS-PHARMACOLOGICAL PROFILE OF MIRTAZAPINE AND ITS ENANTIOMERS

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

Pharmacological indices of side-effects / (Table 3)

The commonly observed side-effects of antidepressants that can be ascribed to receptor interactions are those of anticholinergic (dry mouth, blurred vision, constipation, urinary retention), 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 1 adrenoceptors, as observed in vitro in the labelled prazosin binding assay in rat brain cortex homogenates and in the isolated rat vas deferens assay. On the basis of these observations a low incidence of orthostatic hypotension would be predicted, which is in line with the clinical observations in depressed patients.

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

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

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

The enantiomers of mirtazapine differ considerably with respect to biochemical activity. The α2 -blocking activity of mirtazapine is virtually confined to the (S) + enantiomer, which is also the more potent $5HT_2$ antagonist. However, the (R)-enantiomer is the active principle in mirtazapine with regard to $5HT_3$ antagonistic activity. Both enantiomers contribute to a similar extent to the antihistaminic and (weak) α1-adrenolytic properties of mirtazapine.

Contribution of mirtazapine main metabolites to its pharmacological profile
Demethyl-mirtazapine, the only metabolite found in the rat brain after oral administration of mirtazapine, has anti-anxiety activity in the conflict- punishment test in rats, but is less active in the rat EEG profile for antidepressant activity than the parent compound. The demethyl metabolite is also less active than the parent compound in *in vivo* tests for α2-blocking and $5HT_2$ antagonistic activity. This may be due to poor bioavailability upon systemic administration, since the *in vitro* tests show that the compound is approximately equally active to mirtazapine as an α2 and $5HT_2$ antagonist, important indices for therapeutic antidepressant activity. With respect to antagonism at the histamine H_1 receptor, which is probably related to sedation, the demethyl metabolite appears to be less active than the parent compound.

8-hydroxy-mirtazapine, 8-hydroxy demethyl mirtazapine and N(2)-oxide of mirtazapine have not been found to penetrate into the rat brain and are inactive in vivo, with the exception of the N(2)-oxide and the 8-hydroxy metabolite, which display some anti-serotonergic activity. In vitro, these metabolites are much less active than the parent compound at important receptors, like the α2, $5HT_2$ and histamine H_1 receptors. They are, therefore, not considered to be relevant for the pharmacodynamic profile of mirtazapine, with regard to therapeutic activity or side-effects.

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

Cardiovascular pharmacology of mirtazapine

Cardiovascular effects

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

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

Hemodynamic effects

In anesthetized dogs mirtazapine, at 0.1 mg/kg i.v., does not induce any hemodynamic changes; at 1.0 mg/kg i.v., slightly decreases heart rate and myocardial contractility and slightly increases peripheral vascular resistance; at 10 mg/kg i.v., mirtazapine induces a slight decrease in heart rate and stroke index resulting in a slightly decreased cardiac index, a decrease in myocardial contractility and an increase in peripheral vascular resistance resulting in decreased femoral and common carotid blood flow.

Cardiotoxicity

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

TOXICOLOGY

Acute toxicity

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

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

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

Repeated dose toxicity

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

Subchronic toxicity

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

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

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

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

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

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

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

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

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

have taken place due to overloading with the high dose of the test material. As in the subchronic thirteen-week study, tubular vacuolation and brown pigmentation were reversed during the one-month recovery period.

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m2 basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma infemales at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known.

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

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

Impairment of Fertility: In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg (20 times the maximum recommended human dose (MRHD) on a mg/m^2 basis). Mating

and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD.

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PART III: CONSUMER INFORMATION

PrRhoxal-mirtazapine FC
mirtazapine

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

ABOUT THIS MEDICATION

What the medication is used for:
PrRhoxal-mirtazapine FC is for the symptomatic relief of depressive illness.

When it should not be used:
Do not use Rhoxal-mirtazapine FC if you are allergic to it or any of the components (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.

What the medicinal ingredient is:
Mirtazapine

What the important nonmedicinal ingredients are:
15 mg tablets: Lactose monohydrate, colloidal silicon dioxide, pregelatinized starch, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, iron oxide yellow, polysorbate 80.

30 mg tablets: Lactose monohydrate, colloidal silicon dioxide, pregelatinized starch, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, iron oxide yellow, polysorbate 80. FD & C yellow No. 6, iron oxide red.

What dosage forms it comes in:
Tablets: 15 mg and 30 mg

WARNINGS AND PRECAUTIONS

BEFORE you use PrRhoxal-mirtazapine FC talk to your doctor if:

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

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

Avoid alcoholic drinks while taking Rhoxal-mirtazapine FC.

Contact your physician before stopping or reducing your dosage of Rhoxal-mirtazapine FC. 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 Rhoxal-mirtazapine FC. 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 Rhoxal-mirtazapine FC to alleviate the symptoms.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medications (prescription and non-prescription) and dietary supplements you are using.

You should avoid taking St. John's Worth if you are taking Rhoxal-mirtazapine FC.

PROPER USE OF THIS MEDICATION

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

Never increase or decrease the amount of Rhoxal-mirtazapine FC you are taking unless your doctor tells you to and do not stop taking this medication without consulting your doctor. (see under Precautions when taking Rhoxal-mirtazapine FC).

Some symptoms may begin to improve within about two (2) 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). You should swallow the tablets whole with water. Do not chew them.

Do not split the 15 mg tablets.

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.

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

Overdose:
If you have taken a large number of pills all 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.

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

- You may experience some side effects such as increase in appetite, weight gain, drowsiness or sleepiness, swollen ankles or feet, occasional dizziness or faintness (especially when you

get up quickly from a lying or sitting position) and headache. In rare cases other effects may include seizures, attack of mania, yellow colouring of eyes or skin, rash, abnormal sensation in the skin (e.g., burning, stinging, tickling or tingly) or restless legs. Some side effects are temporary. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

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

HOW TO STORE IT

- Store at room temperature, 15-30˚C in the original package. Keep tightly closed and protect from light.
- Keep Rhoxal-mirtazapine FC out of reach of children.
- Do not use Rhoxal-mirtazapine FC after the expiry date indicated on the package.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll free telephone: 866-234-2345
toll free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Canada
Address Locator: 0701C
Ottawa, ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, was prepared by Rhoxalpharma Inc. for health professionals.

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