MIRTAZAPINE (Systemic)

Category

Antidepressant.

Indications

Accepted

Depressive disorder, major (treatment)¾Mirtazapine is indicated for the treatment of depression 1.

The effectiveness of using mirtazapine for longer than 6 weeks has not been evaluated in controlled trials 1.

Pharmacology

Mechanism of action/Effect:

The exact mechanism of action is unknown 1.

Evidence indicates that mirtazapine may enhance central noradrenergic 1 and serotonergic 1 activity, possibly through its antagonist activity at central presynaptic alpha 2-adrenergic inhibitory autoreceptors and heteroreceptors 1.

Mirtazapine shows no significant affinity for serotonin 5-HT 1A or 5-HT 1B receptors 1.

Other actions/effects:

Mirtazapine is a potent antagonist at serotonin 5-HT 2 and 5-HT 3 receptors, and a moderate antagonist at muscarinic receptors 1.

Mirtazapine produces sedative effects due to potent histamine H 1 receptor antagonism 1 , and orthostatic hypotension due to moderate peripheral alpha 1-adrenergic receptor antagonism 1.

Precautions to Consider

Carcinogenicity/Tumorigenicity

Carcinogenicity studies in mice given doses of 2, 20, and 200 mg per kg of body weight per day (mg/kg/day), which is up to 20 times the maximum recommended human dose (MRHD) of 45 mg per day (mg/day) on a mg per square meter of body surface area (mg/m 2) basis, found an increase in hepatocellular adenomas and carcinomas in male mice in the high dose group 1.

Carcinogenicity studies in rats given doses of 2, 20, and 60 mg/kg/day, which is up to 12 times the MRHD on a mg/m 2 basis, found an increase in hepatocellular adenomas in females at the middle and

high doses, and an increase in hepatocellular tumors and thyroid follicular adenomas/cystadenomas and carcinomas in males at the high dose 1.

These effects may have been mediated by nongenotoxic mechanisms 1 , the relevance of which to humans is unknown 1.

Mutagenicity

Mirtazapine had no mutagenic or clastogenic effects, and did not induce general DNA damage based on the Ames test, the in vitro gene mutation assay in Chinese hamster V 79 cells, the in vitro sister chromatid exchange assay in cultured rabbit lymphocytes, the in vivo bone marrow micronucleus test in rats, and the unscheduled DNA synthesis assay in HeLa cells 1.

Pregnancy/Reproduction

Fertility¾When given mirtazapine doses that were three or more times the MRHD of 45 mg/day on a mg/m 2 basis, rats showed disrupted estrous cycling 1.

Also, in rats given mirtazapine doses that were 20 times the MRHD on a mg/m 2 basis, preimplantation fetal losses occurred 1.

Mating and conception in rats were not affected by mirtazapine 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done.
Studies in pregnant rats and rabbits given mirtazapine doses of up to 20 and 17 times the MRHD on a mg/m 2 basis, respectively, showed no teratogenic effects 1.

However, in rats receiving 20 times the MRHD on a mg/m 2 basis, there were an increase in postimplantation fetal losses, a decrease in pup birth weights, and an increase in pup deaths during the first 3 days of lactation 1.

The cause of these deaths is unknown 1.

FDA Pregnancy Category C 1.

Labor and delivery¾The effect of mirtazapine on labor and delivery is unknown.

Breast-feeding

It is not known whether mirtazapine is distributed into breast milk 1.

Pediatrics

No information is available on the relationship of age to the effects of mirtazapine in pediatric patients. Safety and efficacy have not been established 1.

Geriatrics

No geriatrics-specific problems that would limit the usefulness of mirtazapine in the elderly were seen in studies that included elderly subjects 1.

However, mirtazapine clearance was reduced by 40% in elderly males, and by 10% in elderly females as compared with younger males and younger females, respectively 1.

Also, elderly patients are more likely to have age-related renal function impairment, which may decrease mirtazapine clearance 1.

Pharmacogenetics

Mirtazapine exhibits a longer half-life in females than in males across all age groups 1.

The mean elimination half-life was found to be 37 hours in females, and 26 hours in males 1.

Also, in elderly females, mirtazapine clearance was reduced by 10%, while in elderly males clearance was reduced by 40% 1.

However, responsiveness to mirtazapine therapy showed no age or gender differences 1 , and initial dosing recommendations are the same for all adult patients 1, 2.

Dental

Prolonged use of mirtazapine may decrease or inhibit salivary flow, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Alcohol 1 or

>> CNS depression-producing medications 1 , other (see Appendix II)

(CNS depressant effects of these medications and mirtazapine are additive 1 ; concurrent use is not recommended 1)

Antihypertensive medications 1

(hypotensive effect of these medications or mirtazapine may be enhanced 1)

Enzyme inducers 1 , hepatic, cytochrome P450 (see Appendix II) or

Enzyme inhibitors 1 , hepatic, various (see Appendix II)

(in vitro studies have shown mirtazapine to be a substrate for cytochrome P450 isoenzymes CYP2D6, CYP1A2, and CYP3A4 1 ; metabolism and pharmacokinetics of mirtazapine may be affected by induction or inhibition of these isoenzymes 1)

>> Monoamine oxidase (MAO) inhibitors 1 , including furazolidone, procarbazine, and selegiline

(serious, sometimes fatal reactions have occurred in patients taking MAO inhibitors in combination with, or soon after discontinuing, other antidepressant medications 1 ; symptoms have included autonomic instability with rapid fluctuation of vital signs 1 , diaphoresis 1 , dizziness 1 , flushing 1 , hyperthermia 1 , mental status changes ranging from agitation to coma 1 , myoclonus 1 , nausea 1 , rigidity 1 , seizures 1 , tremor 1 , and vomiting 1 ; although there is no experience with the combination in humans, use of mirtazapine concurrently with an MAO inhibitor, or within 14 days of discontinuing therapy with an MAO inhibitor is contraindicated 1 ; also, MAO inhibitor therapy should not be initiated within 14 days of the discontinuation of mirtazapine 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 1

(during premarketing studies, increases in ALT [SGPT] to ³ three times the upper limit of normal were seen in 2% of patients receiving mirtazapine as compared with 0.3% of patients receiving placebo 1 ; while these increases were clinically significant, and led to discontinuation of mirtazapine in some patients, most of these patients did not develop signs or symptoms of decreased hepatic function 1 ; in some patients, ALT [SGPT] levels returned to normal with continued use of mirtazapine 1)

Cholesterol, total 1

(during premarketing studies, increases in nonfasting cholesterol to ³ 20% above the upper limits of normal were seen in 15% of patients receiving mirtazapine as compared with 7% of patients receiving placebo 1)

Triglycerides, serum 1

(during premarketing studies, increases in nonfasting triglyceride to ³ 500 mg per deciliter were seen in 6% of patients receiving mirtazapine as compared with 3% of patients receiving placebo 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Hypersensitivity to mirtazapine 1

Risk-benefit should be considered when the following medical problems exist

Cardiovascular or cerebrovascular disease that could be exacerbated by hypotension, such as history of myocardial infarction, angina, or ischemic stroke 1 or

Conditions that would predispose patients to hypotension, such as dehydration or hypovolemia 1

(mirtazapine showed a significant orthostatic hypotensive effect in early trials with normal volunteers; however, during premarketing studies, this effect was seen less frequently in depressed patients 1)

Drug abuse or dependence, or history of 1

(patients with a history of drug abuse should be observed closely for signs of misuse or abuse of mirtazapine, as with any new central nervous system [CNS] drug 1)

>> Hepatic function impairment 1

(significant alanine aminotransferase [ALT (SPGT)] elevations [³ three times the upper limit of normal] occurred in some patients with normal liver function while they were receiving mirtazapine in premarketing studies 1 ; most of these patients did not develop signs or symptoms of decreased hepatic function, but the increases in ALT [SGPT] levels led to discontinuation of mirtazapine in some patients 1 ; in other patients, ALT [SGPT] levels returned to normal with continued use of mirtazapine 1 ; mirtazapine should be used with caution in patients with impaired hepatic function 1)
(clearance of a single 15-mg oral dose of mirtazapine was reduced by 30% in patients with hepatic function impairment as compared with clearance in patients with normal hepatic function 1)

Mania or hypomania, or history of 1

(mania or hypomania has occurred rarely in patients treated with mirtazapine 1)

Renal function impairment 1

(the clearance of a single 15-mg oral dose of mirtazapine was reduced by about 30% in patients with moderate renal function impairment [glomerular filtration rate (GFR) = 11 to 39 mL per minute per 1.73 square meters of body surface area (mL/min/1.73m 2)], and by about 50% in patients with severe renal function impairment [GFR < 10 mL/min/1.73m 2] 1)

Seizures, history of 1

(one patient experienced a seizure during premarketing clinical trials of mirtazapine; there are no controlled studies of mirtazapine use in patients who have a history of seizures 1)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Careful supervision of depressed patients with suicidal tendencies 1

(recommended especially during early treatment phase before peak effectiveness of mirtazapine is achieved 1 ; prescribing the smallest number of tablets necessary for good patient management is recommended to decrease the risk of overdose 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence less frequent

Dyspnea 1 (shortness of breath); edema 1 (swelling); flu-like symptoms 1; hyperkinesia 1 (increased movement); hypokinesia 1 (decreased movement); mood or mental changes, including abnormal thinking 1; agitation 1; anxiety 1; apathy 1; and confusion 1; skin rash 1
Incidence rare

Agranulocytosis 1 or neutropenia 1 chills); (fever; sore throat; sores in mouth)¾may be asymptomatic; facial edema 1 (swelling of face); impotence 1 (decreased sexual ability); menstrual changes 1 (painful menstruation; absence of menstruation); mood or mental changes, including delusions 1; depersonalization 1; emotional lability 1; hallucinations 1; hostility 1; and mania 1; seizures 1

Note: Use of mirtazapine was associated with agranulocytosis in two, and severe neutropenia in one of 2796 patients treated in premarketing clinical studies 1.

Recovery occurred in all three patients after mirtazapine was discontinued 1.

Mirtazapine treatment should be discontinued in any patient who develops fever, sore throat, stomatitis, or other signs of infection and who has a low white blood cell (WBC) count 1.

The patient should then be closely monitored 1.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Constipation 1; dizziness 1; drowsiness 1; dryness of mouth 1; increased appetite 1; weight gain 1

Note: Weight gain led to discontinuation of mirtazapine treatment in 8% of patients enrolled in U.S. premarketing studies 1.

Incidence less frequent

Abdominal pain 1; abnormal dreams 1; asthenia 1 (weakness); back pain 1; hyperesthesia 1 (increased sensitivity to touch); hypotension (low blood pressure); increased thirst 1; myalgia 1 (pain in muscles); nausea 1; orthostatic hypotension 1 (dizziness or fainting when getting up suddenly from a sitting or lying position); tremor 1 (trembling or shaking); urinary frequency 1 (increased need to urinate); vertigo 1 (sense of constant movement of self or surroundings); vomiting 1

Overdose

For specific information on the agents used in the management of mirtazapine overdose, see the Charcoal, Activated (Oral-Local) monograph.
For more information on the management of overdose or unintentional ingestion, contact a poison control center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Acute

Disorientation 1; drowsiness 1; impaired memory 1; tachycardia 1 (fast heartbeat)

Note: Experience with mirtazapine overdose is very limited 1.

Treatment of overdose

Note: The possibility of multiple drug involvement should be considered in managing overdose 1.

There is no specific antidote for mirtazapine 1.

General measures used in the treatment of overdose with any antidepressant should be employed 1.

Monitoring¾Monitoring of cardiac and vital signs is recommended 1.

Supportive care¾Establish and maintain an airway, oxygenation and ventilation 3, 1.

Employ general symptomatic and supportive measures 1.

Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Use in the elderly¾Elderly patients, especially males, may have reduced clearance
Dental¾Possible dryness of mouth; using sugarless candy or gum, ice, or saliva substitute for relief; checking with physician or dentist if dry mouth continues for more than 2 weeksContraindicated medications¾Monoamine oxidase (MAO) inhibitors
Other medications, especially alcohol or CNS depression-producing medications
Other medical problems, especially hypersensitivity to mirtazapine or hepatic function impairment
Proper use of this medication

Taking with or without food, as directed by physician

>> Proper dosing
>> Proper storage
Precautions while using this medication

>> Not using concurrently or within 14 days of discontinuing therapy with an MAO inhibitor; not beginning MAO inhibitor therapy within 14 days of discontinuing therapy with mirtazapine

>> Avoiding use of alcohol or other CNS depression-producing medications

Regular visits to physician to check progress during therapy

>> Checking with physician immediately if any symptoms of infection, especially fever, chills, sore throat, or mucus membrane ulcerations, occur

>> Possible drowsiness, impairment of judgement, thinking, or motor skills 1 ; caution when driving, using machinery, or doing other jobs requiring alertness 1

Possible orthostatic hypotension 1 ; getting up slowly from a lying or sitting position

Side/adverse effects

Signs of potential side effects, especially dyspnea, edema, flu-like symptoms, hyperkinesia, hypokinesia, mood or mental changes, skin rash, agranulocytosis or neutropenia, facial edema, impotence, menstrual changes, and seizures

General Dosing Information

Any symptoms of infection, especially flu-like symptoms, such as fever, chills, or sore throat, or mucous membrane ulcerations, occurring during mirtazapine treatment should be reported to the physician immediately 1.

The patient should be evaluated for possible agranulocytosis 1.

Long-term efficacy of mirtazapine has not been evaluated in controlled trials, and its usefulness as long-term therapy for an individual patient should be evaluated periodically 1.

Diet/Nutrition

Food has a minimal effect on mirtazapine absorption 1.

Oral Dosage Forms

MIRTAZAPINE TABLETS

Usual adult dose

Antidepressant¾
Oral, initially 15 mg once a day, preferably in the evening prior to sleep 1.

The dose may be increased, as needed and tolerated, at intervals of not less than one to two weeks 1.

Usual adult prescribing limits

Up to 45 mg a day 1.

Usual pediatric dose

Safety and efficacy have not been established 1.

Usual geriatric dose

See Usual adult dose 1, 2.

Note: Plasma mirtazapine levels may be higher in elderly patients and in patients with moderate to severe renal or hepatic function impairment than in younger adults without renal or hepatic function impairment because of decreased clearance 1.

Strength(s) usually available

U.S.¾15 mg (Rx)[Remeron (scored) (corn starch) (hydroxypropyl cellulose) (magnesium stearate) (colloidal silicon dioxide) (lactose) 1]

30 mg (Rx)[Remeron (scored) (corn starch) (hydroxypropyl cellulose) (magnesium stearate) (colloidal silicon dioxide) (lactose) 1]

Packaging and storage:

Store between 20 and 25 °C (68 and 77 °F) 1 , unless otherwise specified by manufacturer.

Auxiliary labeling:

· Avoid alcoholic beverages.
· May cause dizziness or drowsiness.