



PRODUCT MONOGRAPH

MANERIX[®]

(moclobemide)

150 mg & 300 mg Tablets

Antidepressant

Hoffmann-La Roche Limited
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Mississauga, Ontario
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Control # 070589

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Manerix[®]

(moclobemide)

Tablets

ACTIONS AND CLINICAL PHARMACOLOGY

MANERIX (moclobemide) is a short-acting, Reversible Inhibitor of Monoamine oxidase type A (RIMA). It is a benzamide derivative which inhibits the deamination of serotonin, noradrenaline and dopamine. This action leads to increased concentrations of these neurotransmitters, which may account for the antidepressant activity of moclobemide.

Monoamine oxidases are currently subclassified into two types, A and B, which differ in their substrate specificity. Moclobemide preferentially inhibits MAO-A; at a 300 mg dose, the inhibition of MAO-A is approximately 80%, while that of MAO-B is approximately 20 - 30%. The estimated MAO-A inhibition is short-lasting (maximum 24 hours) and reversible.

PHARMACOKINETICS

Volunteers

General: Following oral administration, moclobemide is 98% absorbed from the gastrointestinal tract. Due to hepatic first pass effect, absolute bioavailability is approximately 55% after single doses, but 90% after multiple doses. The apparent volume of distribution is approximately 1.2 L/kg, indicating extensive tissue distribution.

Moclobemide is extensively metabolized, largely via oxidative reactions on the morpholine moiety of the molecule. While 95% of the administered dose is excreted in the urine, less than 1% of this is in the unchanged form. Active metabolites recovered *in vitro* or in animal experiments are present only at very low concentrations in the systemic circulation in man. Moclobemide is 50% bound to plasma proteins, mainly to albumin. The presence of food reduces the rate, but not the extent of moclobemide absorption.

Single Dose: Following the administration of a 100 mg single oral dose of moclobemide to healthy subjects, peak plasma concentrations ranged from 488 ng/mL to 1,450 ng/mL (mean C_{max} : 849 ng/mL) and were reached in 0.5 to 3.5 hours (mean T_{max} : 49 min). The elimination half-life is 1.5 hours. Up to 200 mg, the pharmacokinetics of moclobemide are linear. At higher doses, non-linear pharmacokinetics are observed. In a dose range of 400 mg to 1,200 mg, maximum plasma concentrations increased and clearance decreased in a non dose-proportional manner. With increasing doses, the elimination half-life also becomes prolonged.

Multiple Dose: During the second week of a 100 mg t.i.d. dosing regimen in healthy subjects, the steady-state trough concentrations of moclobemide ranged between 114 ng/mL and 517 ng/mL. An increase in the dose to 150 mg t.i.d. resulted in a greater than proportional increase in moclobemide steady-state trough concentrations, namely to concentrations ranging between 346 ng/mL and 1,828 ng/mL.

Patients

Hepatic Impairment, Single Dose: In patients with liver cirrhosis, the administration of a single 100 mg dose of moclobemide resulted in approximately a three-fold increase in peak plasma concentrations (C_{max} : 1,607 ng/mL), and elimination half-life ($t_{1/2\beta}$: 4.0 hr), while clearance decreased about four-fold (Cl 337 mL/min).

Renal Impairment, Single Dose: In patients with renal insufficiency, the administration of a single 100 mg dose of moclobemide did not appreciably alter the pharmacokinetics of the drug, except for an increase in absorption time.

Elderly Patients, Single and Multiple Dose: Following a 100 mg t.i.d. dosing regimen in elderly subjects (65 to 77 years old), C_{max} and AUC values were somewhat higher than in young subjects (21 to 34 years old), namely 1,498 versus 950 ng/mL and 5,571 versus 3,102 ng·h/mL, respectively. Clearance in the elderly was reduced (19.7 versus 32.3 L/h).

Slow Metabolisers: Because moclobemide is partly metabolized by polymorphic isozymes (CYP2C19 and CYP2D6), blood levels of the drug can be affected in patients with genetically or drug-induced poor metabolism. Approximately 2% of the caucasian population and 15% of the asian population can be genetically phenotyped as slow metabolisers with respect to oxidative hepatic metabolism. It was found that the area under the curve (AUC) measurement in slow metaboliser subjects was approximately 1.5 times greater than in extensive metaboliser subjects for the same dose of moclobemide. This increase is within the normal range of variation (up to two-fold) typically seen in patients.

INDICATIONS AND CLINICAL USE

MANERIX (moclobemide) is indicated for the symptomatic relief of depressive illness.

CONTRAINDICATIONS

MANERIX (moclobemide) is contraindicated in patients with a known hypersensitivity to moclobemide or any component of the product. As with any other exogenous compound the possibility of hypersensitivity reaction should be considered in susceptible patients. Symptoms of hypersensitivity may include rash and edema. MANERIX is also contraindicated in patients in an acute confusional state.

In a clinical study designed to test the interaction between MANERIX and a tricyclic antidepressant (clomipramine), severe adverse reactions emerged and the study was terminated. Data involving other tricyclic antidepressants are limited. Consequently, the concomitant use of MANERIX and tricyclic antidepressants is contraindicated.

Clinical data are not available on the concomitant use of MANERIX and selective serotonin reuptake inhibitors or conventional MAO inhibitors. Therefore, until such data become available, MANERIX should not be administered in combination with these agents.

Although there is limited experience with the concomitant use of moclobemide and narcotics, death has occurred in patients receiving a conventional MAO inhibitor and meperidine (pethidine) given concomitantly. Moclobemide should not be used in combination with meperidine. The concomitant use of 'Manerix' and Mellaril (thioridazine) is contraindicated (see PRECAUTIONS).

As the safety and effectiveness of MANERIX in children below the age of 18 have not been established, pediatric use is not recommended.

PRECAUTIONS

General

The possibility of suicide in depressed patients is inherent in their illness and may persist until remission occurs. Therefore, patients must be carefully supervised during all phases of treatment with MANERIX (moclobemide). Prescriptions in potentially suicidal patients should be written for a limited supply only.

In patients with thyrotoxicosis or pheochromocytoma, conventional MAO-inhibitors may precipitate a hypertensive reaction. Because there are no data available on the use of moclobemide in such patients, caution is advised when prescribing MANERIX to these subjects.

Occupational Hazards

Patients should be cautioned against driving an automobile or performing hazardous tasks until they are certain of the effect that MANERIX has on them.

Use in Pregnancy

Safety of use in pregnancy has not been established. Therefore, MANERIX is not recommended in women who may be pregnant, unless, in the opinion of the physician, the expected benefits to the patient markedly outweigh the possible risk to the fetus.

Nursing Mothers

Clinical data suggest that small quantities of moclobemide are excreted in human milk. Therefore, MANERIX is not recommended in nursing mothers unless the anticipated benefits outweigh the potential harm to the infant.

Hepatic Dysfunction

In patients with severe liver dysfunction, the daily dose of MANERIX should be substantially reduced to one-third or one-half of the standard dose (see ACTIONS AND CLINICAL PHARMACOLOGY - PHARMACOKINETICS).

Renal Dysfunction

Single dose pharmacokinetic data suggest that no dosage adjustment may be required in patients with impaired renal function (see ACTIONS AND CLINICAL PHARMACOLOGY - PHARMACOKINETICS). However, multiple dose studies with MANERIX have not been performed in patients with renal dysfunction, therefore, MANERIX should be used with caution in this patient population. In normal volunteers, the absolute bioavailability almost doubles following multiple dosing as compared to a single dose.

Dextromethorphan

Co-administration of moclobemide and dextromethorphan which may be contained in cough and cold medicines is not recommended (see DRUG INTERACTIONS).

Thioridazine

A study to evaluate the potential of moclobemide to inhibit the cytochrome enzyme P4502D6 (P4502D6) concluded that moclobemide can affect the pharmacokinetics of drugs (such as thioridazine) that are mainly metabolized by P4502D6. Thioridazine administration results in a dose-dependent prolongation of the QTc interval, which may cause serious ventricular arrhythmias

including torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with moclobemide-induced inhibition of thioridazine metabolism (see CONTRAINDICATIONS).

DRUG INTERACTIONS

Cimetidine

Cimetidine doubles the AUC (area under the plasma concentration-time curve) of MANERIX (moclobemide) and is expected to approximately double moclobemide steady-state concentrations.

In patients receiving MANERIX concomitantly with cimetidine, a 50% reduction in the dosage of MANERIX may be necessary.

Tyramine

During studies conducted at the maximum recommended moclobemide dose of 600 mg/day, the mean dose of tyramine required to produce a 30 mm Hg increase in systolic blood pressure was 148 ± 50 mg (76 - 200 mg) when moclobemide was administered immediately after tyramine. The threshold dose of tyramine was reduced to 84 ± 23 mg (54 - 112 mg) when the sequence of administration was reversed so that moclobemide was administered one hour before tyramine. These findings indicate that the potentiation of tyramine may be minimized by administering moclobemide after, instead of prior to, a tyramine-enriched meal. There is limited experience in patients who took MANERIX before meals. Most clinical trial protocols specified that the drug be taken immediately after meals. Therefore, patients should be instructed to take MANERIX immediately after meals .

Treatment with MANERIX does not necessitate special dietary restrictions. In clinical studies it was demonstrated that up to 100 mg tyramine can be safely ingested during treatment with 'Manerix' 600 mg/day when 'Manerix' was given after meals. This amount of tyramine, 100 mg, corresponds to 1,000 g to 2,000 g mild or 200 g strong cheese, or to 70 g Marmite yeast extract.

As a safety measure, patients should be urged to report immediately the abrupt occurrence of any of the following symptoms; occipital headache, palpitations, neck stiffness, tachycardia or bradycardia or other atypical or unusual symptoms not previously experienced.

Other Antidepressants

Concomitant Use: Clinical interaction studies between MANERIX and a tricyclic antidepressant (clomipramine) resulted in severe adverse reactions (see CONTRAINDICATIONS). Data involving other tricyclic antidepressants are limited. Therefore, the concomitant use of MANERIX and tricyclic antidepressants is contraindicated.

Clinical data are not available on the concomitant use of MANERIX and selective serotonin reuptake inhibitors, or conventional monoamine oxidase inhibitors. Therefore, until clinical data become available, MANERIX should not be administered in combination with these agents.

Sequential Use: Treatment with a tricyclic antidepressant may be initiated following the discontinuation of MANERIX with a short washout period of no less than two days.

When switching patients from serotonergic antidepressants to a conventional MAO-inhibitor, it is standard practice to allow for a washout period equivalent to at least 4-5 half-lives of the previously administered drug or any active metabolites. This recommendation also applies to MANERIX.

Prozac

An exception is Prozac (fluoxetine); at least five weeks should elapse between its discontinuation and initiation of treatment with MANERIX.

Buspirone

To date, there is no experience regarding the co-administration of MANERIX and buspirone. Therefore, patients should be carefully monitored should concomitant administration be implemented.

Antipsychotics

In depressed patients with schizophrenic or schizoaffective disorder, psychotic symptoms may be exacerbated during treatment with MANERIX. There is little experience regarding the concomitant use of MANERIX and antipsychotic drugs. Therefore, patients should be carefully monitored should concomitant treatment be undertaken.

Thioridazine

A study to evaluate the potential of moclobemide to inhibit the cytochrome enzyme P4502D6 (P4502D6) concluded that moclobemide can affect the pharmacokinetics of drugs (such as thioridazine) that are mainly metabolized by P4502D6. Thioridazine administration results in a dose-dependent prolongation of the QTc interval, which may cause serious ventricular arrhythmias including torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with moclobemide-induced inhibition of thioridazine metabolism (see CONTRAINDICATIONS).

Alcohol

Excessive alcohol consumption should be avoided. Alcohol interaction studies were performed at blood alcohol concentrations of 0.05%. However, no studies were conducted at blood alcohol concentrations recognized as legally intoxicating.

Anesthetic Agents

While specific data on the use of MANERIX in patients undergoing anesthesia are not available, based on its reversible action and short elimination half-life (see ACTIONS AND CLINICAL PHARMACOLOGY) 'Manerix' should be discontinued no less than two days before the administration of anesthetic agents, especially spinal or local anesthetic agents that contain epinephrine.

In animals, moclobemide has been shown to potentiate the effects of opiates. The combination of moclobemide and meperidine (pethidine) is not recommended (see CONTRAINDICATIONS). Other opioid analgesics should be used with extreme caution, if at all, and a dosage adjustment may be necessary for these drugs.

Sympathomimetics

Following multiple oral doses of MANERIX (total dose: 600 mg/day), a phenylephrine -induced increase in systolic blood pressure was potentiated (1.6 times) after intravenous administration. Patients should be advised to avoid the concomitant use of sympathomimetic amines (e.g., amphetamine and ephedrine like compounds contained in many proprietary cold, hay fever or weight-reducing preparations), until further studies have been conducted.

Dextromethorphan

In isolated cases, the co-administration of moclobemide and dextromethorphan resulted in adverse events, including vertigo, tremor, nausea and vomiting. Since cough and cold medicines may contain dextromethorphan, they should not be taken without prior consultation with the physician, such that non-dextromethorphan containing alternatives may be given (see Precautions).

Antihypertensive Agents

Clinical trials with MANERIX have shown inconsistent effects on the blood pressure of hypertensive patients. Therefore, careful monitoring is recommended during initial treatment.

ADVERSE REACTIONS

The following table lists the adverse events reported during clinical trials in which 1,922 patients were treated with 50-600 mg/day MANERIX (moclobemide) for depressive illness. Limited experience in 60 patients treated with 601 to 750 mg/day of MANERIX suggests that the incidence of adverse reactions may increase at higher doses.

Clinical Adverse Events > 1%

| Organ System | Adverse Event | % | |
|------------------------|--|---------------------------|----------------------|
| | | Moclobemide (n = 1922) | Placebo (n = 271) |
| Central Nervous System | headache, pressure in head | 8.0 | 11.1 |
| | insomnia, sleep disturbances | 7.3 | 4.8 |
| | dizziness | 5.1 | 8.1 |
| | tremour | 5.0 | 3.0 |
| | increased agitation | 4.5 | 2.6 |
| | restlessness, nervousness | 4.1 | 2.6 |
| | sleepiness, somnolence | 3.7 | 5.5 |
| | tiredness, sedation | 3.0 | 4.1 |
| | increased anxiety, acute anxiety state | 2.8 | 2.2 |
| | weakness or faintness | 1.2 | 1.8 |
| Gastrointestinal | nausea | 5.2 | 4.8 |
| | constipation | 3.9 | 3.3 |
| | gastrointestinal pain, epigastric discomfort | 2.3 | 2.6 |
| | sickness | 1.9 | 1.1 |
| | diarrhea | 1.8 | 1.1 |
| | abdominal fullness, abdominal pain | 1.6 | 1.5 |
| | vomiting | 1.6 | 0.4 |
| Cardiovascular | tachycardia, palpitations | 3.8 | 3.3 |
| | hypotension | 3.0 | 0.4 |
| | orthostatic, reactive hypotension | 2.3 | 3.3 |
| Anticholinergic | dry mouth | 9.2 | 10.7 |
| Miscellaneous | sweating | 2.4 | 2.2 |
| | blurred vision | 1.8 | 1.1 |
| | increase/loss of appetite | 1.3 | 1.8 |

Other clinical adverse events with an incidence of < 1% in clinical studies, or reported in post-marketing surveillance, are as follows:

Psychiatric: Difficulties falling asleep, nightmares/dreams, hallucinations, memory disturbances, confusion, disorientation, delusions, increased depression, excitation/irritability, hypomanic symptoms, aggressive behaviour, apathy, tension.

Central and Peripheral Nervous System: Migraine, extrapyramidal effects, tinnitus, paresthesia, dysarthria.

Gastrointestinal: Heartburn, gastritis, meteorism, indigestion.

Cardiovascular: Hypertension, bradycardia, extrasystoles, angina/chest pain, phlebitic symptoms, flushing.

Dermatological/Mucocutaneous: Exanthema/rash, allergic skin reaction, itching, gingivitis, stomatitis, dry skin, conjunctivitis, pruritus, urticaria.

Genito-Urinary: Disturbances of micturition (dysuria, polyuria, tenesmus) metrorrhagia, prolonged menstruation.

Miscellaneous: General malaise, skeletal/muscular pain, altered taste sensations, hot flushes/cold sensation, photopsia, dyspnea, visual disturbances.

Laboratory Abnormalities

Laboratory examinations were performed in a total of 1,401 patients during clinical trials with MANERIX. Reductions were observed in leucocyte, SGOT and SGPT values, however, these reductions were attributed to raised baseline values returning to normal, and were not considered clinically relevant. No other laboratory abnormalities were noted during clinical trials.

In post-market surveillance, there appeared to be a low incidence of raised liver enzymes, without associated clinical sequelae.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Signs and symptoms of overdose with MANERIX (moclobemide) include nausea, vomiting, drowsiness, disorientation, slurred speech, amnesia, reduced reflexes, agitation, hypertension and convulsions. One patient remained stuporous for 36 hours following an overdose with 1,550 mg MANERIX. All abnormal laboratory values and vital signs returned to within normal range one to five days after overdose. No organ toxicity was reported.

Treatment

The treatment of overdose should consist of general supportive measures. Gastric lavage or induction of emesis, activated charcoal and fluid control may be of benefit.

As with other antidepressants, mixed overdoses of moclobemide with other drugs (e.g. agents active on the CNS), could be life-threatening. Serotonergic syndrome and death have been reported after combined overdose of moclobemide and other antidepressants. Therefore, such patients should be closely monitored so that appropriate care and treatment may be given.

DOSAGE AND ADMINISTRATION

NOTE: MANERIX (moclobemide) should always be taken after meals (see DRUG INTERACTIONS).

Usual Adult Dosage

The administration of MANERIX should be initiated at 300 mg daily dose (in two divided doses), and increased gradually to a maximum of 600 mg/day if needed, noting carefully the clinical response and any evidence of intolerance. Individual patient response may allow for a reduction of the daily dose. As with other antidepressants, it should be kept in mind that there may be a lag time in therapeutic response. There is no evidence that increasing the dosage rapidly shortens this latent period and may, in fact, increase the incidence of side-effects. Furthermore, because bioavailability of moclobemide has been shown to increase over the first week of dosing (see PHARMACOKINETICS), the initial daily dose of 300 mg should not be increased until after this first week of therapy.

Liver Dysfunction

When hepatic metabolism is severely impaired by hepatic disease or inhibited by a drug that affects microsomal mixed function oxidase activity (e.g. cimetidine), the daily dose of MANERIX should be reduced to one-third or one-half of the standard dose.

Renal Dysfunction

Single dose pharmacokinetic data suggest that no dosage adjustment may be required in patients with impaired renal function. However, multiple dose studies with MANERIX have not been performed in patients with renal dysfunction, therefore, MANERIX should be used with caution in this patient population. In normal volunteers, the absolute bioavailability almost doubles following multiple dosing as compared to a single dose.

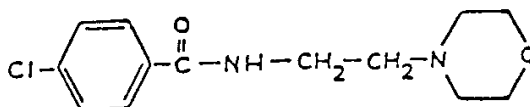
Elderly

No dosage adjustments are necessary in elderly patients.

Cimetidine

Cimetidine doubles the AUC (area under the plasma concentration-time curve) of MANERIX and is expected to approximately double moclobemide steady-state concentrations (see DRUG INTERACTIONS).

In patients receiving MANERIX concomitantly with cimetidine, a 50% reduction in the dosage of MANERIX may be necessary.

PHARMACEUTICAL INFORMATIONi) **Drug Substance:****Proper Name:** moclobemide**Chemical Name:** p-chloro-N-(2-morpholinoethyl)benzamide**Structural Formula:****Molecular Formula:** C₁₃H₁₇ClN₂O₂**Molecular Weight:** 268.74

Description: Moclobemide is an almost white crystalline powder with a faint odour. It is slightly soluble in water. pK_a is approximately 6.2. The partition coefficient in a pH 7.4 octanol/buffer solution at 22°C is approximately 40. The melting point is approximately 138°C.

ii) **Composition:**

Each film-coated tablet contains either 150 mg or 300 mg moclobemide. The non-medical ingredients are as follows:

150 mg tablets: cornstarch, ethylcellulose, iron oxide, lactose, magnesium stearate, methylhydroxypropyl cellulose, polyethylene glycol, povidone, sodium starch glycolate, talc, titanium dioxide.

300 mg tablets: cornstarch, ethylcellulose, lactose, magnesium stearate, methylhydroxypropyl cellulose, polyethylene glycol, povidone, sodium starch glycolate, talc, titanium dioxide.

iii) **Stability and Storage Recommendations:**

Store at 15-30°C.