

PRODUCT MONOGRAPH

PrMOCLOBEMIDE

Moclobemide Tablets

100 mg, 150 mg and 300 mg

Antidepressant

**AA PHARMA INC.
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ACTIONS AND CLINICAL PHARMACOLOGY

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.

Comparative Bioavailability

Two comparative bioavailability studies were performed using healthy human volunteers. The rate and extent of absorption of moclobemide was measured and compared after administration of a single oral dose of 1) Moclobemide or Manerix 150 mg tablets after a 10 hour fast, and 2) Moclobemide or Manerix 300 mg tablets after a standardized meal. The results are summarized as follows:

Fasting Study: Summary Table of the Comparative Bioavailability Data
Moclobemide (Dose: 1x150 mg) From Measured Data

| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Geometric Means (%)** | 90% CI** |
|--------------------------------|---|-------------------|-----------------------------------|--------------|
| | Moclobemide | Manerix+ | | |
| AUC _T (ng hr/mL) | 2592 2920 (46) | 2671 3053 (49) | 97.7 | 94.2 – 101.3 |
| AUC _I (ng hr/mL) | 2760 3133 (48) | 2840 3275 (52) | 97.8 | 94.2 – 101.5 |
| C _{max} (ng/mL) | 773 836 (39) | 748 823 (39) | 103.3 | 93.6 - 114.1 |
| T _{max} (hr)* | 2.09 (63) | 1.78 (40) | -- | -- |
| t _{1/2} (hr)* | 1.84 (31) | 1.83 (30) | -- | -- |

* Arithmetic means (CV%).

** Based on the least square estimate of the geometric means.

+ Manerix (Hoffmann-La Roche Ltd.) was purchased at a Canadian retail pharmacy.
Manerix is currently sold in Canada by Valeant Canada LP

| Fed Study: Summary Table of the Comparative Bioavailability Data Moclobemide (Dose: 1x300 mg) From Measured Data | | | | |
|---|---|-------------------|-----------------------------------|---------------|
| Parameter | Geometric Mean Arithmetic Mean (CV%) | | Ratio of Geometric Means (%)** | 90% CI** |
| | Moclobemide | Manerix+ | | |
| AUC _T (ng\$hr/mL) | 8144 9189 (50) | 7801 8782 (54) | 104.3 | 97.9 – 111.2 |
| AUC _I (ng\$hr/mL) | 8708 10121 (59) | 8350 9712 (62) | 104.2 | -- |
| C _{max} (ng/mL) | 2065 2179 (32) | 1861 1958 (33) | 111.0 | 100.5 – 122.5 |
| T _{max} (hr)* | 1.92 (53) | 2.25 (44) | -- | -- |
| t _{1/2} (hr)* | 2.34 (45) | 2.35 (45) | -- | -- |

* Arithmetic means (CV%).

** Based on the least square estimate of the geometric means.

+Manerix (Hoffmann-La Roche Ltd.) was purchased at a Canadian retail pharmacy.
Manerix is currently sold in Canada by Valeant Canada LP

INDICATIONS AND CLINICAL USE

Adults

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

Pediatrics < 18 years of age: the safety and efficacy of MOCLOBEMIDE (moclobemide) has not been established in the pediatric population, therefore its use is not recommended.

CONTRAINDICATIONS

MOCLOBEMIDE (moclobemide) is contraindicated in the following circumstances:

- 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. In patients in an acute confusional state.
- Concomitantly with tricyclic/tetracyclic antidepressants (see DRUG INTERACTIONS, Other Antidepressants).
- In combination with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or conventional monoamine oxidase inhibitors (MAO-Is) (see DRUG INTERACTIONS, Other Antidepressants).
- In combination with selegiline (see DRUG INTERACTIONS)
- In combination with meperidine.

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.

- Concomitantly with thioridazine. (see PRECAUTIONS and DRUG INTERACTIONS).
- Concomitantly with dextromethorphan (contained in many proprietary cough medicines).
- In combination with Bupropion
- In combination with Triptans
- In combination with Tramadol

WARNINGS

Potential Association with the Occurrence of Behavioural and Emotional Changes, Including Self-Harm

It is unknown whether increased risk of suicidal ideation and behaviour is associated with the use of older antidepressants (eg moclobemide) in pediatric patients and/ or adults. However, recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggest that use of these drugs may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo. Thus, rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages given any antidepressant drug. This

includes monitoring for emotional and behavioural changes.

PRECAUTIONS

General

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 MOCLOBEMIDE 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 MOCLOBEMIDE has on them.

Use in Pregnancy

Safety of use in pregnancy has not been established. Therefore, MOCLOBEMIDE 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, MOCLOBEMIDE is not recommended in nursing mothers unless the anticipated benefits outweigh the potential harm to the infant.

Angle-Closure Glaucoma

As with other antidepressants, moclobemide can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Hepatic Dysfunction

In patients with severe liver dysfunction, the daily dose of MOCLOBEMIDE 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 moclobemide have not been performed in patients with renal dysfunction, therefore, MOCLOBEMIDE 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.

Thioridazine

A study to evaluate the potential of moclobemide to inhibit the cytochrome enzyme P45002D6 (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 and DRUG INTERACTIONS).

DRUG INTERACTIONS

Selegiline

Studies revealed that the combination of moclobemide and selegiline had a supra-additive effect to the tyramine sensitivity. The tyramine sensitive factor was increased with an individual variability. It was expected that the effect of oral tyramine might potentiate this effect to an even greater extent. It was therefore concluded that food containing tyramine should be omitted. Under daily conditions an absolute omission of food with tyramine is almost impossible. Based on the individual variability of the increase in sensitivity it is also not possible to recommend a specific amount which would be still well tolerated. Therefore the combination of moclobemide and selegiline is contraindicated.

Linezolid

Linezolid is a reversible, non-selective inhibitor of MAO and its use is contraindicated in combination with MOCLOBEMIDE.

Cimetidine

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

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

Triptans

Triptans are potent serotonin receptor agonists indicated for the treatment of migraine. In general, triptans are metabolized by monoamine oxidases (MAOs) and various cytochrome P450 enzymes. Concomitant use of MOCLOBEMIDE with a triptan can lead to potentially harmful exposure to the triptan or its active metabolite. Due to these characteristics, the concomitant use of triptans with MOCLOBEMIDE is contraindicated (See Contraindications).

Trimipramine and Maprotiline

The concomitant use of MOCLOBEMIDE with Trimipramine and Maprotiline can result in an increase of their plasma concentrations. As Trimipramine and Maprotiline are non-selective monoamine reuptake inhibitors, their plasma concentration elevation may increase monoamine concentration to a level that can lead to severe adverse events (e.g. serotonin syndrome). Therefore, combination of Trimipramine/Maprotiline and MOCLOBEMIDE is contraindicated.

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 moclobemide before meals. Most clinical trial protocols specified that the drug be taken immediately after meals. Therefore, patients should be instructed to take MOCLOBEMIDE immediately after meals.

Treatment with MOCLOBEMIDE 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 moclobemide 600 mg/day when moclobemide 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 moclobemide and a tricyclic antidepressant (clomipramine) resulted in severe adverse reactions (see CONTRAINDICATIONS). Data involving other tricyclic/tetracyclic antidepressants are limited. Therefore, the concomitant use of MOCLOBEMIDE and tricyclic/ tetracyclic antidepressants is contraindicated.

Clinical data are not available on the concomitant use of moclobemide and selective serotonin re-uptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRIs), or conventional monoamine oxidase inhibitors (MAOI-Is). Therefore, until clinical data becomes available, MOCLOBEMIDE should not be administered in combination with these agents.

Sequential Use: Treatment with a tricyclic antidepressant may be initiated following the discontinuation of moclobemide 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 MOCLOBEMIDE.

Prozac

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

Drugs metabolised by CYP2C19

Care should be taken with concomitant use of drugs that are metabolised by CYP2C19 as moclobemide is an inhibitor of this enzyme. The plasma concentration of these drugs (e.g. proton pump inhibitors (PPIs), some antiepileptic or other CYP2C19 substrates) may be increased when concomitantly used with moclobemide. In CYP2C19 extensive metabolisers, the use of the PPI omeprazole resulted in a twofold AUC increase of moclobemide. Similarly, moclobemide inhibits the metabolism of omeprazole in CYP2C19 extensive metabolisers resulting in a doubling of the omeprazole exposure.

Buspirone

To date, there is no experience regarding the co-administration of moclobemide 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 MOCLOBEMIDE. There is little experience regarding the concomitant use of moclobemide 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 moclobemide in patients undergoing anesthesia are not available, based on its reversible action and short elimination half-life (see ACTIONS AND CLINICAL PHARMACOLOGY), MOCLOBEMIDE 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 moclobemide (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

MOCLOBEMIDE should not be co-administered with dextromethorphan as isolated cases of severe central nervous system adverse reactions have been reported after co-administration (See CONTRAINDICATIONS).

Antihypertensive Agents

Clinical trials with moclobemide 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 moclobemide for depressive illness. Limited experience in 60 patients treated with 601 to 750 mg/day of moclobemide 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 |
| | | nausea | 5.2 |

| Organ System | Adverse Event | % | |
|------------------|--|-------------------------|--------------------|
| | | Moclobemide (n=1922) | Placebo (n=271) |
| Gastrointestinal | 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.

Cases of suicidal ideation and suicidal behaviours have been reported during antidepressant therapy or early after treatment discontinuation (see WARNINGS).

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 moclobemide. 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

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

Symptoms

Signs and symptoms of overdose with 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 of 1,550 mg moclobemide. 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: MOCLOBEMIDE (moclobemide) should always be taken after meals (see DRUG INTERACTIONS).

Usual Adult Dosage

The administration of MOCLOBEMIDE should be initiated at 300 mg daily dose (in 2 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 MOCLOBEMIDE 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 moclobemide have not been performed in patients with renal dysfunction, therefore, MOCLOBEMIDE 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 MOCLOBEMIDE and is expected to approximately double moclobemide steady-state concentrations (see DRUG INTERACTIONS).

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

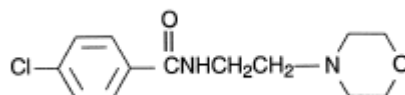
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: moclobemide

Chemical Name: p-chloro-N-(2-morpholinoethyl)benzamide

Structural Formula:



Molecular Formula: C₁₃H₁₇ClN₂O₂

Molecular Weight: 268.74 g/mol

Description: Moclobemide is an almost white crystalline powder with a faint odour. It is slightly soluble in water. The 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.

Composition

In addition to moclobemide, each 100 mg and 150 mg film-coated tablet contains the non-medicinal ingredients (in alphabetical order): carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dextrates, hydroxypropyl methylcellulose, iron oxide yellow, magnesium stearate, polydextrose, polyethylene glycol (carbowax) and titanium dioxide. The 100 mg tablet also contains iron oxide red.

In addition to moclobemide, each 300 mg film-coated tablet contains the non-medicinal ingredients (in alphabetical order): colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

Stability and Storage Recommendations

Store at room temperature (15°C -30 °C.)

AVAILABILITY OF DOSAGE FORMS

MOCLOBEMIDE 100 mg: Each orange, oval, biconvex, film-coated tablet, scored on one side and engraved “100” on the other, contains moclobemide 100 mg. Available in bottles of 100.

MOCLOBEMIDE 150 mg: Each pale yellow, oval, biconvex, film-coated tablet, scored on one side and engraved “150” on the other, contains moclobemide 150 mg. Available in bottles of 100.

MOCLOBEMIDE 300 mg: Each white, oval, biconvex, film-coated tablet, scored on one side and engraved “300” on the other, contains moclobemide 300 mg. Available in bottles of 100.

PHARMACOLOGY

ANIMAL

Pharmacodynamics

In vitro, Ex vivo

Liver and brain tissue homogenates were incubated with moclobemide and tested with the MAO substrates serotonin (5-HT) and phenylethylamine (PEA) in order to characterize moclobemide as an inhibitor of MAO-A or MAO-B, respectively (Table 1).

Table 1: In vitro and ex vivo MAO Inhibition in Liver and Brain Tissue Homogenates

| Homogenate | Man | | Rat | |
|---|------|--------|------|-----|
| | 5-HT | PEA | 5-HT | PEA |
| Liver | 12 | >1,000 | 4 | 220 |
| Brain | 11 | >1,000 | 8 | 70 |
| (<u>In vitro</u> , IC ₅₀ , μmol/L) | | | | |
| Brain | | | 10 | 98 |
| (<u>Ex vivo</u> , ED ₅₀ , μmol/kg p.o.) | | | | |
| | | | | |

| | Man | | Rat | |
|---|-----|--|-----------|-----------------|
| Liver | | | 0.5 - 0.9 | 9 - 12 |
| Brain | | | 5.0 - 7.5 | 110- \geq 200 |
| (Ex vivo, ED ₅₀ , μ mol/kg i.p.) | | | | |

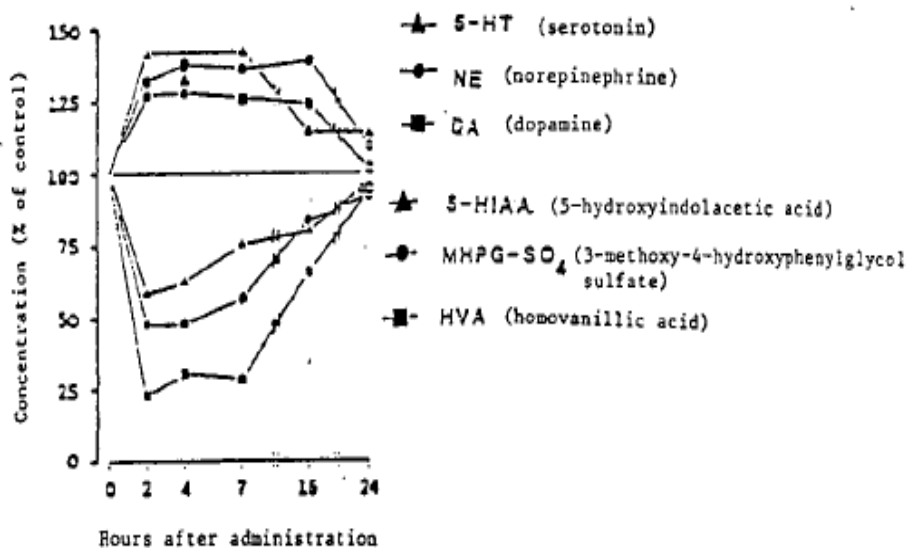
In in vitro rat brain models, moclobemide had no effect on the synaptosomal uptake of serotonin, dopamine and norepinephrine.

In vivo

After the administration of a 50 mg/kg oral dose of moclobemide to rats, slight elevations in cerebral norepinephrine, dopamine and serotonin concentrations, lasting 16 hours, were observed. Values had returned to control levels by 24 hours after administration.

Concentrations of the monoamine metabolites were reduced maximally by two and seven hours after administration but had returned to control levels by 24 hours. (Figure 1)

Figure 1: Changes in activities of brain monoamines and their metabolites with time after oral administration of 50 mg/kg moclobemide in rat. Points represent percentages of controls (saline) and are means of five single values.



Moclobemide was also active in animal models considered predictive for antidepressant activity:

1. It reversed monoamine releser-induced sedation and ptosis in mice with a duration of action of less than 16 hours (ED₅₀ = 30 mg/kg i.p.).

2. In cats, moclobemide dose-dependently suppressed REM sleep ($ED_{50} = 18.6$ mg/kg i.p.) without disturbing the sleep-wakefulness cycle (10-30 mg/kg i.p.), and
3. In the behavioural despair test in mice, moclobemide decreased the immobility score ($ED_{120} = 43$ mg/kg). In addition, moclobemide potentiated the 5-hydroxytryptophan-induced behavioural triad (head twitching, tremours and abduction) in mice ($ED_{50} = 1.0$ mg/kg i.p.).

Drug Interactions

A 100 mg/kg p.o. single dose of moclobemide potentiated the effects of single dose meperidine, morphine and dextropropoxyphene in groups of 10 mice. Following repeated dosing with analgesics, no significant potentiation was observed. In groups of 6 rats, there was no acute interaction between moclobemide and hydroflumethiazide, but sodium excretion was increased following the repeated administration of 100 mg/kg p.o. moclobemide. Moclobemide (100 mg/kg p.o.) potentiated the anti-inflammatory action of ibuprofen in groups of 5 rats. A possible antagonism was found with ouabain (mice) and prazosin (rats). An antagonism with furosemide was observed (rats).

Pharmacokinetics

The pharmacokinetic profile of moclobemide was determined in rats and dogs. Following oral administration, moclobemide was rapidly absorbed, reaching peak concentrations within 10 minutes in rats and 0.5-1 hour in dogs. A hepatic first-pass effect reduced absolute bioavailability to 10-20% and 67% in rats and dogs, respectively. In dogs, maximum plasma concentrations increased proportionately with increasing doses (5-100 mg/kg) and declined with a terminal half-life of approximately 1-2 hours. Distribution and metabolism were extensive in both species; only 1-3% of the dose was recovered in urine as intact drug. The major route of elimination after metabolism was via the kidneys. Approximately 66-90% of the administered dose was recovered in the urine, primarily within the first 24 hours. The main urinary metabolites in rat were the N-oxide metabolite (13%), p-chlorohippuric acid (11%) and the secondary amine (8%). In dogs, p-chlorohippuric acid, the secondary amine and the N-oxide accounted for 36%, 22% and 7% of the dose, respectively. The protein binding of moclobemide in plasma from dogs ranged from 27% to 44%.

TOXICOLOGY

Acute Toxicity

| | | LD₅₀ (moclobemide) | | |
|----------------|-------------------|--------------------------------------|------------------------------------|---------------------------|
| Species | Strain | Route | LD₅₀ (mg/kg) | Observation Period |
| Mice | Fü SPF | oral i.p. | 1,141 572 | 24h + 10 days |
| | Charles River CFI | oral i.p. s.c. | 730-800 450-530 940- >1,000 | 14 days |
| Rats | Fü SPF | oral i.p. | 4,138-4,444 678 | 24h + 10 days 10 days |
| | Charles River CD | oral i.p. | 1,300 530 | 14 days |
| Rabbits | New Zealand White | oral | 800 | 14 days |

Most frequently observed signs and symptoms were decreased motor activity, muscle relaxation, respiratory depression, loss of righting reflex, ataxia, sedation, hypnosis, salivation, tonic-clonic convulsions, tremors, and corneal opacity.

Subacute Toxicity

In an oral pyramiding dose toxicity study, moclobemide was dispersed in starch, encapsulated and administered to four dogs (two/sex) at doses of 0 (starch capsule) 3, 10, 30, 100, 300 and 1,000 mg/kg.

The dogs were essentially asymptomatic following doses of 3, 10, 30 and 100 mg/kg. After the 300 mg/kg dose, three dogs exhibited emesis. There was a slight 34% reduction in food consumption in female dogs and the platelet count of all dogs was slightly elevated (24%). Following the administration of the 1,000 mg/kg dose, all four dogs exhibited emesis, excessive salivation, decreased motor activity and half-shut eyes. Three dogs had tremors and two of four dogs were dazed, ataxic and displayed jerking movements of the head. One dog was disoriented and exhibited lacrimation. Food consumption was markedly reduced (92%) in male dogs but only slightly decreased (42%) in female dogs; food consumption returned to pretreatment levels

one day after dosing. The platelet count was slightly elevated one (20%) and seven (22%) days after the final dose.

Long-term Toxicity

Long-term toxicology studies have been conducted in rats and dogs:

| Species | Route of Admin. | Maximum Dose (mg/kg) | Treatment Duration |
|---------|-----------------|----------------------|--------------------|
| Rats | i.v. | 50 | 4 weeks |
| | p.o. | 300 | 14 weeks |
| | p.o. | 270 | 26 weeks |
| | p.o. | 250 | 18 months |
| Dogs | i.v. | 50 | 4 weeks |
| | p.o. | 200 | 12 weeks |
| | p.o. | 100 | 26 weeks |
| | p.o. | 125 | 12 months |

Rats

1. Four-Week I.V.

Moclobemide (25 mg/mL) was administered intravenously for four weeks to rats (12/sex/group) at doses of 0 (saline control), 10, 20 or 50 mg/kg/day.

The 50 mg/kg/day dose produced tonic-clonic convulsions immediately after injection (males only), followed by slight sedation lasting approximately 30 minutes (males and females) and one male death. A moderate dose-dependent reduction in body weight gain (15% at the highest dose) was seen in male rats.

2. Fourteen-Week Oral

Moclobemide was administered as a dietary admixture for fourteen weeks to rats (6/sex/group) at doses of 0 (controls), 30, 100 or 300 mg/kg/day.

Food consumption and body weight gain were reduced in a dose-dependent manner; at the highest dose, weight gains of 15-60 g were noted compared to increases of 101-229 g in the control group. Immediate moderate to large weight gains occurred at the end of the 14-week treatment period.

The slight increases in GOT, GPT, alkaline phosphatase and blood sugar observed in all treated groups relative to controls were considered not to be drug-related. Administration of 100 or 300 mg/kg/day dose of moclobemide was associated with a slight transient depression of total serum protein in male rats. A small delay in bromsulphalein elimination was observed in week 12 in two female rats receiving the 100 mg/kg/day dose.

3. Twenty-Six Week Oral

Moclobemide was administered as a dietary admixture for 26 weeks to rats (20/sex/group) at doses of 0 (control), 30, 90, 270 mg/kg/day.

Slight piloerection was periodically observed in high-dose animals from day 30 onward. Bodyweight gains were reduced in a dose-related manner; at the highest dose, male and female bodyweights were 61% and 71% of controls, respectively.

Increases in hemoglobin and mean cell hemoglobin concentration (MCHC) were evident in treated animals of both sexes after 6 weeks of treatment. In most cases these increases, which ranged from 2-16% above control values, were statistically significant. Similar increases (2-11%) were seen in high dose animals of both sexes after 13 and 24 weeks of treatment. All treated females showed increases in GOT after 2 and 6 weeks that were statistically significantly different from controls in most cases. A similar pattern was evident in middle and high dose females after 13 weeks. These increases ranged from 14-41% above control values. After 24 weeks, GOT values in treated females were within normal range.

Macroscopic examination at necropsy revealed a slightly increased incidence of gastrointestinal reddening in treated animals, particularly in males. Small spleens were occasionally noted, predominantly in high-dose females. The majority of absolute organ weights showed statistically significant reductions in treated animals associated with the reduced bodyweight gain. Treatment related increases in relative organ weights were observed in lungs (7-24%), kidneys (4-12%), thyroids (14-43%; males only) and gonads (0-56%).

4. 18 -Month Oral

Moclobemide was administered as a dietary admixture for 18 months to rats (20/sex/group) at doses of 0 (controls), 10, 50 or 250 mg/kg/day.

Body weight development was dose dependently retarded in both sexes. Blood chemistry examinations showed a slight tendency to minimally increased alkaline phosphatase and GPT values in rats treated with 250 mg/kg/day moclobemide.

In male rats receiving 250 mg/kg/day moclobemide, relative heart and liver weights (adjusted to a body weight of 100 g) were reduced by 8.3% and 12.8%, respectively, compared to controls.

In

females of the same dosage group, adjusted relative ovary and brain weights were decreased 16.8% and 32.1%, respectively, compared to controls.

Dogs

1. Four-Week I.V.

Moclobemide (25 mg/mL) was administered intravenously for four weeks to dogs (3/sex/group) at doses of 0 (saline control), 12.5, 25 or 50 mg/kg/day.

During the first days of the experiment, animals treated with 25 mg/kg/day moclobemide became slightly sedated shortly after drug administration. Moderate to marked sedation, lasting one to two hours after injection, was noted in the 50 mg/kg/day dosage group throughout the study. CNS-related head-shaking was also observed at this dose.

2. Twelve-Week Oral

Moclobemide capsules were administered for twelve weeks to dogs (4 males and 2 females/group) at doses of 0 (empty capsule), 20, 60 or 200 mg/kg/day.

Dogs administered 60 mg/kg/day moclobemide had a 5% weight loss during the first weeks of the study. Ten to fifteen percent reductions in RBC counts, hematocrit and hemoglobin occurred in some of the dogs in this group. Biochemically, only plasma cholesterol values were affected, decreasing slightly in some of the dogs.

At the 200 mg/kg/day dosage, dogs showed immediate, severe weight losses amounting to approximately 10% per week for the first two weeks. After six weeks of moclobemide administration, body weights of five of the six animals in this group were decreased to 60 to 70% of their starting weights. Moclobemide administration was stopped, and three dogs were sacrificed due to cachexia. In the three remaining dogs, immediate and rapid weight gains were observed following treatment discontinuation. In one week, the body weights of these animals were increased to 25% above their weights at six weeks.

Reductions of approximately 25% in RBC counts, hematocrit and hemoglobin concentrations were observed after six weeks of the 200 mg/kg/day moclobemide dose. Slight increases in GOT and GPT, a reduction in plasma cholesterol concentration, a slowing of the heart rate and lengthening of the QT interval, very low heart weights in two dogs, and slight atrophy of the myocardial fibers were also observed at this dose. After three weeks without moclobemide, these changes showed marked improvement.

3. Twenty-Six Week Oral

Moclobemide capsules were administered for twenty-six weeks to dogs (4/sex/group) at doses of 0 (empty capsule), 10, 30 or 100 mg/kg/day.

Dogs administered 100 mg/kg/day moclobemide began to lose weight from week six, and body weights remained virtually constant until study termination. However, moclobemide had no effect on the consumption of food and water.

Moderate dose-related decreases in hemoglobin concentration, RBC count, and PCV were noted at week six. These decreases were statistically significant in dogs administered 100 mg/kg/day moclobemide. This effect was less marked during the remainder of the study, but decreases were also statistically significant in females in the high-dose group at weeks 13, 18 and 24. A dose-related reduction in plasma cholesterol concentrations was observed in female dogs; decreases in this parameter were statistically significant at the high dose throughout the study, at 30 mg/kg/day after weeks 13 and 18, and at the low dose after 13 weeks.

At the high-dose, absolute uterus weights decreased, and absolute liver weights increased in males. Relative liver weights were increased at 30 and 100 mg/kg/day; relative thyroid and adrenal weights were increased at the high dose, and relative lung weights were increased at all three moclobemide doses. Decreased relative uterus weights were seen in the high-dose group.

Microscopic examination of tissue sections revealed the following:

- a Anestrus, characterized by an absence of normal reproductive-cycle changes in the uteri, ovaries and mammary glands of all female dogs administered 100 mg/kg/day moclobemide.
- b Minimal hepatic fibrosis, indicative of low-grade liver injury, occurring in three males and three females in the high-dose group, and in one of four females given 30 mg/kg/day moclobemide.
- c A minimal increase in the incidence and severity of thymic regression in male dogs in the high-dose group.

4. Twelve-Month Oral

Moclobemide capsules were administered for 12 months to dogs (5/sex/group) at doses of 0 (empty capsule), 5, 20 or 100/125 mg/kg/day. As a result of good tolerance, the dose in group four was increased from 100 mg/kg/day to 125 mg/kg/day after six months. One dog of each sex from each dosage group continued to be examined for an additional six weeks after drug administration ended (recovery period).

At the highest dose, a moderate 10-20% reduction in RBC counts, hemoglobin and PCV was observed in females after 9 and 12 months of moclobemide administration. These values remained within the lower limit of the physiological range during the study and returned to normal during the recovery period. Mean triglyceride values were minimally increased in males and decreased in females. Cholesterol levels were minimally to moderately decreased (20-40%) in both sexes at most examinations. Alkaline phosphatase showed a tendency to higher values in males. Triglyceride, cholesterol and alkaline phosphatase values returned to normal during the recovery period.

At the highest dose, liver and adrenal weights were increased. Histological examination of the liver revealed a slight increase in hemosiderin deposits relative to other groups, especially in females. Minimal fibrosis was observed in five dogs and an additional case occurred in one animal administered 5 mg/kg/day.

Mutagenicity

Ames Test

In the Ames test, with and without metabolic activation, moclobemide concentrations of 0.02-20 mg/plate were not mutagenic for Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100.

Micronucleus Test (Mouse Bone Marrow)

Moclobemide did not induce chromosomal breakage or mitotic non-disjunctions in mouse bone marrow after a single dose of 800 mg/kg by gavage.

Hamster V-79/HGPRT Assay

Moclobemide concentrations of 1.0-4.0 mg/mL (without metabolic activation) or 2.0-3.4 mg/mL (with metabolic activation) did not induce forward mutations at the HGPRT locus in Chinese Hamster V79 cells.

Induction of Chromosomal Aberations (Human Lymphocytes)

Moclobemide concentrations of 200-600 mg/mL (without metabolic activation) or 600-4,000 mg/mL (with metabolic activation) did not induce chromosomal damage in human peripheral lymphocytes.

Unscheduled DNA Synthesis (Rat Hepatocytes)

Moclobemide did not induce DNA damage resulting in unscheduled DNA synthesis, in freshly isolated rat hepatocytes at 0.1-2.0 mg/mL, or in cultured human fibroblasts at 0.4-1.2 mg/mL.

Carcinogenicity

1. Eighty Week Oral – Mice

An 80 week oral (dietary admixture) carcinogenicity study with moclobemide was conducted in mice (50/sex/group) at doses of 0 (control-1), 0 (control-2), 10, 50 or 250 mg/kg/day.

Body weight development was similar for both male and female mice at moclobemide doses of 10 and 50 mg/kg/day. At 250 mg/kg/day, body weights were reduced by 10% relative to the other groups. Relative kidney weights in the highest dose group were increased approximately 15% compared to control animals.

Neoplastic lesions were observed in the lungs, hemolymphoreticular system, liver, ovaries, and pituitary gland in both control and treatment groups. The incidences of lesions which occurred more frequently in treated animals than in controls are summarized below:

| | Lungs Bronchioalveolar Tumours | | Hemolymphoreticular System Malignant Lymphomas | Liver Adenomas |
|-----------|--------------------------------|---------|--|----------------|
| | (Females) | (Males) | (Males) | (Males) |
| Control-1 | 33% | 52% | 4% | 4% |
| 10 | 36% | 46% | 10% | 14% |
| 50 | 40% | 52% | 8% | 14% |
| 250 | 57% | 38% | 4% | 16% |
| Control-2 | 42% | 36% | 2% | 12% |

The dose-related increase in pulmonary tumors observed in females did not reach statistical significance. The neoplastic lesions noted in this study were considered to reflect the spectrum of spontaneous neoplasms usually observed in mice of this strain and age.

2. Two Year Oral – Rats

A two-year oral (dietary admixture) carcinogenicity study was conducted in rats (50/sex/group) at moclobemide doses of 0 (control-1), 0 (control-2), 9, 45 or 225 mg/kg/day.

Thirty-seven males and 60 females died prematurely. In both sexes, survival was greater at 45 and 225 mg/kg/day moclobemide than at 0 and 9 mg/kg/day. The negative dose-related trend was significant for males and for both sexes combined.

A total of 136 rats, 71 males and 65 females, had foci or hyperplasia. The clearest effect of treatment was for hepatocellular hyperplasia. Of the 23 cases reported, one occurred in the combined control groups, none was seen at 9 mg/kg, 7 occurred at 45 mg/kg and 15 at 225 mg/kg. The dose-related trend was similar and highly significant in each sex individually. The increases reached statistical significance at a moclobemide dose of 225 mg/kg for males and females individually and at 45 mg/kg for both sexes combined.

An increased incidence of alveolar foam cell aggregates was noted in the lungs of male rats at the 45 and 225 mg/kg/day doses and in females at the 9, 45 and 225 mg/kg/day doses. In addition, an increased incidence of small clusters of greenish-brown pigmented alveolar macrophages was diagnosed in the males receiving 225 mg/kg/day. Microscopic examination revealed no qualitative morphological differences between the alveolar macrophages of treated and control rats. The number and size of type II pneumocytes, however, were increased in treated rats compared to controls.

Reproduction and Teratology

1. Fertility and General Reproductive Performance

A fertility and reproductive performance study was conducted in rats at oral (gavage) doses of 15, 40 or 100 mg/kg/day. Thirty-six males were treated 70 days prior to and during mating and 36 females for 14 days prior to mating until the 22nd day of lactation.

Nervousness and salivation were observed in both sexes. No treatment-related parental mortality occurred. The median weight gain of parental males in the 100 mg/kg dose group was significantly reduced throughout the first three weeks of treatment. A slight decrease in median body weight at weaning was observed in dams in the 40 mg/kg dose group. The body weights of females in the 100 mg/kg dose group were decreased throughout most of the treatment period.

Mating success, gestation length, and pregnancy outcome were not influenced by treatment in any group. A slight decrease in the median number of corpora lutea per pregnant female in the two upper dose groups was considered not to be drug-related.

Embryonic and fetal resorption rates were comparable to controls in all dose groups. In the highest dose group, the number of pups born alive was slightly decreased. Median body weights of the F-1 pups were comparable to controls in all dose groups during the lactation period.

The survivability of the F-1 pups was slightly to moderately reduced in the 40 and 100 mg/kg dose group, respectively. The examination of pups which died during the lactation period and of pups in the necropsy sub-groups revealed no abnormality considered to be drug-related.

When the rats from the F-2 generation were mated, the number of implantations, resorptions, and pups born were comparable to controls in all dose groups. At lactation days 1 and 4, a delay in pup weight development and a reduction in survivability were observed in the 100 mg/kg group.

The tests for physical and functional development as well as those for learning and memory revealed no statistically significant findings.

2. Embryotoxicity and Teratology - Rats (Oral)

A teratology study was performed in 40 mated female rats at oral (gavage) doses of 25, 70 or 200 mg/kg/day from day 7 to day 16 of gestation inclusively. Another group of 40 rats received only the vehicle and served as control animals. On the 21st day of gestation, the rats in each dosage group were allocated to either a necropsy or a rearing subgroup.

During the treatment period, maternal weight gain was slightly retarded in the 25 and 70 mg/kg/day groups and moderately reduced in the 200 mg/kg group; by day 17 of gestation, dam weight gains in the low and mid-dose groups were approximately 72-85% of control values. In the high-dose group, dam weight gains were approximately 44% of control values. The reproductive process was not impaired in any of the dosage groups.

In the rearing experiment, there was no indication of a postnatal effect caused by drug administration at 25 or 70 mg/kg/day. At the 200 mg/kg/day dose, the survivability of the pups during the lactation period was reduced slightly to 85%.

The examination of skeletal abnormalities revealed no findings deviating from the norm except an increased number of incised vertebral bodies and poorly ossified sternebrae in the higher dosage groups. These findings indicate a slight retardation of ossification. An examination of soft tissue revealed no malformations in the groups given drug at 25 and 200 mg/kg/day. In the mid-dose group, two fetuses had an enlarged renal pelvis, one fetus had an enlargement of the right lateral cerebral ventricle, and one fetus had exencephaly and spina bifida. Due to their infrequent occurrence, these malformations are considered to be of a spontaneous nature.

3. Embryotoxicity and Teratology - Rabbits (Oral)

A teratology study was performed in 20 mated female rabbits at oral (gavage) doses of 15, 40 or 100 mg/kg/day from day 7 to day 19 of gestation, inclusively. Another group of 20 rabbits received vehicle only and served as controls. The dams were sacrificed on day 30 of gestation and examined for drug effects on fertility and fetal gross abnormalities.

A dose-related retardation of maternal weight gain was observed during the treatment period; by day 20 of gestation, dam weight gains were 85%, 68% and 51% of control values in the low, mid and high dose groups, respectively.

The reproductive process (mean number of corpora lutea and implantations) was not impaired in any of the dosage groups). In the 15 mg/kg/day group, the resorption rate was significantly higher than in controls (33.6% of implantations versus 12.6% of implantations). As the number of resorptions in the higher dosage groups was significantly lower than in the 15 mg/kg group, and within the control range, this finding may not be drug-related. In the 100 mg/kg group, three dams aborted a total of 19 fetuses, two of the dams had severe diarrhea before aborting. One dam in each of the 15 mg/kg and the 40 mg/kg groups aborted.

Detailed examinations of the fetuses for skeletal abnormalities revealed that one fetus in the 40 mg/kg group had a missing medulla oblongata; omphalocele occurred in one fetus in the 15 mg/kg group and in one fetus in the 40 mg/kg group; and in the 40 mg/kg group, four fetuses in one litter had a thick, flatulent abdomen; one fetus had a protruding tongue. Due to their infrequent occurrence at low dosages only, these malformations are considered to be of a spontaneous nature.

4. Perinatal and Postnatal - Rats (oral)

A perinatal and postnatal study was performed in 24 mated female rats/group at oral (gavage) doses of 30, 70 or 150 mg/kg/day from day 16 of gestation up to the end of the lactation period (day 23). Another group of 24 rats received the vehicle only and served as control.

Alopecia and mild transient diarrhea were observed in single animals of all treatment groups including controls, and were therefore regarded as not treatment related. Weight development was slightly delayed in dams in the 150 mg/kg dose group throughout the entire treatment period. No drug-related maternal death was observed. Reproductive parameters were not affected by treatment, with the exception of a slight nonsignificant increase in the resorption rate of dams in the 150 mg/kg dose group.

The median weight development of the F-1 pups during the lactation period was slightly delayed in all dose groups. A slight decrease in pup survivability was observed in the highest dose group. No treatment related gross external or visceral abnormalities were observed in living or dead pups. Tests of the physical and functional development of the F-1 generation revealed no statistically significant findings in any dose group.

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PART III: CONSUMER INFORMATION**PrMOCLOBEMIDE
(Moclobemide)****100 mg, 150 mg and 500 mg Tablets**

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

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

MOCLOBEMIDE is a prescription medication used to treat the symptoms of depression in adults more than 18 years of age.

What it does:

MOCLOBEMIDE is a short-acting antidepressant and belongs to the family of drugs called Reversible Inhibitor of Monoamine Oxidase-type A (RIMA). MOCLOBEMIDE inhibits the imbalance of certain chemicals in the brain by increasing their concentrations. This action accounts for the antidepressant activity of MOCLOBEMIDE.

When it should not be used:

- Do not take MOCLOBEMIDE if:
- You have known allergy to moclobemide or to any of the other ingredients MOCLOBEMIDE contains.
- You suffer from a mental problem that makes you confused, lose contact with reality or unable to think and judge clearly
- You are currently taking a medication to treat depression (a tricyclic/tetracyclic antidepressant, a selective serotonin reuptake inhibitor (SSRI), a serotonin- norepinephrine reuptake inhibitor (SNRI) or a conventional monoamine oxidase inhibitor (MAO-I)).
- You are currently taking selegiline
- You are currently taking the pain medications meperidine or tramadol
- You are currently taking thioridazine
- You are currently taking a migraine medication such as rizatriptan, sumatriptan or other triptans
- You are currently taking bupropion (WELLBUTRIN or ZYBAN).
- You are currently taking dextromethorphan
- You have a pheochromocytoma (a tumor of the adrenal gland)

What the medicinal ingredient is:

Moclobemide

What the nonmedicinal ingredients are:

Each 100 mg and 150 mg film coated tablet contains the non medicinal ingredients (in alphabetical order): carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dextrates, hydroxypropyl methylcellulose, iron oxide yellow, magnesium stearate, polydextrose, polyethylene glycol (carbowax) and titanium dioxide. The 100 mg tablet also contains iron oxide red.

Each 300 mg film coated tablet contains the non medicinal ingredients (in alphabetical order): colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol and titanium dioxide.*Iron oxide is present in the 150 mg tablets only.

What dosage forms it comes in:

MOCLOBEMIDE is available in 100 mg (orange), 150 mg (pale yellow) and 300 mg (white), single scored, biconvex, film-coated tablets.

WARNINGS AND PRECAUTIONS

MOCLOBEMIDE is not for use in children under 18 years of age.

New or Worsened Emotional or Behavioral Problems:

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

MOCLOBEMIDE may take from a few days to several weeks to be really effective, so patience is needed to give the drug a chance to work.

Do not drive a vehicle or perform hazardous tasks until you know how MOCLOBEMIDE affects you.

Effects on Pregnancy and Newborns:

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

MOCLOBEMIDE can cause an acute attack of glaucoma. Seek immediate medical attention if you experience eye pain, changes in vision, swelling or redness in or around the eye.

BEFORE you use MOCLOBEMIDE talk to your doctor or pharmacist if:

- you have ever had a bad reaction to MOCLOBEMIDE or any of the inactive ingredients.
- you are allergic to other medicines, food and dyes.
- you are taking ANY other medicines (prescription or nonprescription) particularly cimetidine, meperidine, selegiline, thioridazine, buspirone, clomipramine, anesthetics, other antidepressants, blood pressure medications, or medications used to treat certain mental illnesses other than depression.
- you are planning to take cough and cold medications containing dextromethorphan or allergy medications.
- you experience psychotic symptoms or are taking antipsychotic medication
- you will be undergoing anesthesia or are taking/will be taking opioid pain medications
- you have any other illnesses/diseases, including a history of liver or kidney disease, thyroid disorders, heart problems, or high blood pressure.
- you are pregnant, plan on becoming pregnant, or are breastfeeding.
- you have a habit of excessive alcohol consumption or street drug use.

This information will help your doctor decide whether you should use MOCLOBEMIDE and what extra care may need to be taken while you are on the medication. You should always consult your doctor or pharmacist before using other medications while on MOCLOBEMIDE.

INTERACTIONS WITH THIS MEDICATION

The following list includes some, but not all, of the drugs that may increase the risk of side-effects while receiving MOCLOBEMIDE. You should check with your doctor or pharmacist before taking any other medication (prescription, non-prescription or natural/herbal such as St John’s Wort) with MOCLOBEMIDE.

- alcohol,
- anesthetics,
- buspirone,
- cimetidine
- clomipramine,
- meperidine,
- selegiline,
- thioridazine,
- other antidepressants,

- medications used to treat certain mental illnesses other than depression.
- blood pressure medications, cough and cold medications containing dextromethorphan,
- allergy medications or any medication that contains amphetamine and ephedrine like compounds
- There are no dietary restrictions but excessive amounts of some foods should be avoided such as over 200g of strong cheese or 70g of Marmite yeast extract

PROPER USE OF THIS MEDICATION

Usual adult dose:

The recommended starting dose of MOCLOBEMIDE is 300 mg/day (150 mg tablet twice a day). Your doctor may recommend to increase the dose to a maximum of 600 mg/day (300 mg tablet twice a day).

MOCLOBEMIDE should always be taken after meals.

MOCLOBEMIDE should be swallowed whole with water. MOCLOBEMIDE tablets should not be split, crushed, chewed or dissolved as this can destroy it or change its effects.

Take MOCLOBEMIDE as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.

It is very important that you do NOT stop taking MOCLOBEMIDE as soon as you start to feel feeling better. Discuss with your doctor how long drug treatment should continue, especially if you have had more than one episode of depression.

Overdose:

If you think you have taken too much MOCLOBEMIDE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs and symptoms of overdose with MOCLOBEMIDE include:

Nausea, vomiting, drowsiness, confusion, slurred speech, memory impairment, reduced reflexes, agitation, increased blood pressure, and seizures.

Missed Dose:

If you forget to take a dose of MOCLOBEMIDE take it as soon as possible, then just carry on with the regular times you take your medication. If you remember your missed dose close to the time for your next dose, do not take the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT

THEM

Like all medications, MOCLOBEMIDE can cause some side effects. Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking MOCLOBEMIDE.

Call your doctor immediately if a combination of the following symptoms occurs:

- Severe throbbing headache which starts at the back of the head and radiates forward
- Neck stiffness
- Heart fluttering, fast or slow heart beat

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|--|---|---|--------------|--|
| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and seek immediate medical help |
| | | Only if severe | In all cases | |
| Common | Insomnia, dizziness, nausea, headache | | ✓ | |
| Rare | Allergic reaction: skin rash or hives, difficulty breathing, swelling of your face, lips, tongue, or throat | | | ✓ |
| Unknown | Fast, racing, pounding or irregular heartbeat | | | ✓ |
| | Slow heartbeat | | ✓ | |
| | Neck stiffness, severe throbbing headache - starting at the back of the head and radiating forward | | ✓ | |
| | Changes in eyesight (vision) | | ✓ | |
| | Diarrhoea or Constipation | | ✓ | |
| | Not enough sodium in your blood. Signs of this may be feeling sleepy, confused or having fits (seizures). | | ✓ | |
| | Feeling confused and lost (disoriented) | | ✓ | |
| | New or Worsened Emotional or Behavioral Problems | thoughts or talk of death or suicide; thoughts or talk of self harm or harm to others; any recent attempts of self-harm | | ✓ |

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

HOW TO STORE IT

Store MOCLOBEMIDE at room temperature between 15°C to 30°C.

Do not use MOCLOBEMIDE tablets after the expiry date. All expired medications should be returned to your pharmacist.

Keep MOCLOBEMIDE and all other medications out of the sight and reach of children

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

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

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

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