

APO-MOCLOBEMIDE

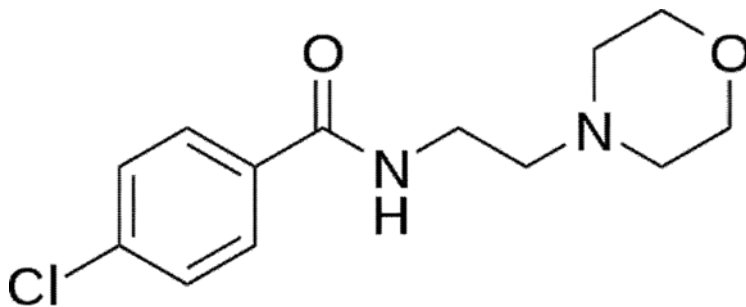
1. APO-MOCLOBEMIDE (150mg and 300mg film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Moclobemide 150mg

Moclobemide 300mg

Chemical Structure:



Molecular Formula: C₁₃H₁₇ClN₂O₂

Excipient with known effect

Apo Moclobemide is gluten and lactose free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-MOCLOBEMIDE 150mg tablets are oval, biconvex tablets, film coated yellow and identified APO over 150 on one side and scored on the other. Each tablet contains 150mg moclobemide and typically weighs 402mg.

APO-MOCLOBEMIDE 300mg tablets are white, oval, biconvex, film coated tablets identified APO over 300 on one side and scored on the other. Each tablet contains 300mg moclobemide and typically weighs 400mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Apo-Moclobemide is indicated in the treatment of depressive syndromes and social phobia.

4.2 Dose and method of administration

Dose

Apo-Moclobemide should be taken after meals.

The dose does not need to be specially adjusted in elderly patients or patients with impaired renal function.

When hepatic function is severely impaired or inhibited by medication that inhibits microsomal mixed function oxidase e.g. cimetidine, the daily dose should be reduced to half or one third.

Depressive syndromes:

The recommended daily dose range is 300-600mg. Treatment with moclobemide can begin with the full therapeutic dose of 300-450mg daily taken in two or three divided doses. With severe depression the dose can be increased to 600mg/day.

The dose should not be increase until after the first week, as bioavailability increases during this period. The individual response may allow a reduction in the daily dose.

Treatment should continue for at least 4-6 weeks in order to assess efficacy.

Social phobia:

The recommended daily dose is 600mg given in 2 divided doses. Treatment with 600mg/day should continue for 8-12 weeks in order to assess the efficacy of the medicine. Social phobia may be a chronic condition and it is reasonable to consider continuation of treatment for a person responding to treatment.

Long-term study results indicate that the efficacy of treatment with moclobemide is maintained with continued use. Periodic evaluation of patients is recommended to establish if further treatment is required.

Use in Children and Adolescents (under 18 years of age):

Safety and efficacy have not been established in this population. Consequently, moclobemide should not be used in patients under 18 years of age (see Special Warnings and Precautions).

Method of administration

See dose.

4.3 Contraindications

- Known hypersensitivity to moclobemide
- Acute confusional states
- Co-administration with selegiline
- Moclobemide should not be used in paediatrics, as clinical experience of the medicines action in children is lacking.
- Co-administration with clomipramine should be avoided due to the risks of increased incidence of adverse effects.

4.4 Special warnings and precautions for use

Clinical Worsening and Suicide Risk:

Patients of any age with Major Depressive Disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressive medications, and this risk may persist until significant remission occurs. Patients should be closely monitored, especially at the beginning of therapy or when the dose is changed, until improvement occurs.

There has been a long-standing concern that some antidepressants may have a role in the emergence of suicidality in some patients.

The possible risk of increased suicidality in patients applies to all classes of antidepressant medicines, as available data are not adequate to exclude this risk for any antidepressant. Therefore, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Generally, when stopping an antidepressant, doses should be tapered rather than stopped abruptly.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric.

Although a causal link between emergence of such symptoms and either the worsening or depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patients presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Mania and Bipolar Disorder:

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that Moclobemide is not approved for use in treating bipolar depression.

Excitation / Agitation:

Depressed patients with excitation or agitation as the main clinical feature may require the addition of benzodiazepines.

Schizophrenic symptoms:

Moclobemide therapy may exacerbate the schizophrenic symptoms of depressive patients with schizophrenic or schizoaffective psychoses. Therapy with long-acting neuroleptics should be continued in such patients, if possible.

Dietary Restrictions:

Special dietary restrictions are not generally required with Moclobemide therapy. However, hypersensitivity to tyramine may exist in some patients and patients should be advised to avoid the consumption to large amounts of tyramine-rich foods.

Hypersensitivity:

Symptoms of hypersensitivity reactions may occur and include rash and oedema.

Theoretical pharmacological considerations indicate that MAO inhibitors may precipitate a hypertensive reaction in patients with thyrotoxicosis or pheochromocytoma. Because experience with Moclobemide therapy in this population group is lacking, caution should be exercised with regard to prescribing Apo-Moclobemide.

Additional medicines which enhance serotonin e.g. many other antidepressants, particularly in multiple combinations, should be given with caution. This is particularly true for clomipramine (see Contraindications, Section 4.3).

Cardiac disorders:

Cases of QTc prolongation and Torsades de Pointes (TdP), have been reported in association with excessive doses of moclobemide.

Therefore moclobemide should be used with caution in patients with risk factors for QTc prolongation including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of moclobemide, and the concomitant use of other QTc prolonging medicines (see Interaction with other medicines and other forms of interaction, Section 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Information for Patients and Families:

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to this medicine's efficacy and safety when used in the treatment regimen proposed.

4.5 Interaction with other medicines and other forms of interaction

Dextromethorphan

Isolated cases of severe, central nervous system adverse reactions (giddiness, light-headedness and agitation) have been reported after co-administration of moclobemide and dextromethorphan. Since some cough and cold medicines may contain dextromethorphan, they should not be taken without prior consultation with a physician.

Selegiline

Co-administration of moclobemide and selegiline is contraindicated due to the relative loss of selectivity if both monoamine oxidase A and B are inhibited.

Opiates

In animals, moclobemide potentiates the effects of opiates. A dosage adjustment of these medicines may be required. Concomitant administration of pethidine and moclobemide should be avoided or carried out only with caution.

Cimetidine

Reduced moclobemide clearance occurred in healthy subjects with combined administration of moclobemide and cimetidine. If moclobemide treatment is initiated in patients pretreated with cimetidine the lowest dose should be given initially. If cimetidine has to be given after initiation of moclobemide therapy, it may be necessary to lower the moclobemide dose by 50% and to adjust according to clinical requirement.

Tyramine

Moclobemide's propensity to interact with tyramine is slight and short lasting, as pharmacological studies in animals and man have shown (see Special Warnings and precautions for use, Section 4.4). The potentiation of the pressor effect was even lower or did not occur when moclobemide was administered after a meal. An interaction with tyramine rich foods is of no clinical importance during moclobemide therapy under normal conditions and if moclobemide is taken at the end of a meal.

Serotonin reuptake inhibitors and tricyclic antidepressants

In patients receiving moclobemide, additional medicines that enhance serotonin, such as many other antidepressants, particularly in multiple combinations, should be given with caution.

This is particularly true for clomipramine. In isolated cases there has been a combination of serious signs and symptoms, including hyperthermia, confusion, hyperreflexia and myoclonus, which are indicative of serotonergic overactivity (serotonergic syndrome).

If these combined symptoms occur, the patient should be closely observed by a physician (hospitalised if necessary) and appropriate treatment given. Treatment with tricyclic or other antidepressants could be initiated immediately after withdrawal of moclobemide (i.e. without a wash out period) and vice versa, provided similar caution is observed. When switching to moclobemide, the dose should not exceed 300mg/day during the first week.

Sympathomimetics

The pharmacological action of systemic regimens of sympathomimetic amines e.g. amphetamine and ephedrine, may be intensified and prolonged by concurrent administration of moclobemide.

Antihypertensives

Clinical trials with moclobemide have shown inconsistent effects on the blood pressure of hypertensive patients. Careful monitoring is recommended during initial treatment.

Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (eg torsades de pointes) is likely to be increased with concomitant use of other medicines which prolong the QTc interval (eg some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval (see Special warnings and precaution for use, Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3.

Reproduction studies in animals have not revealed any risk to the foetus but the safety of moclobemide in human pregnancy has not been established. The potential benefits of therapy during pregnancy should be weighed against the possible risk to the foetus.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of antidepressants in pregnancy.

Neonates exposed to antidepressants, late in the third trimester have shown drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of antidepressants in pregnancy may be associated with an increase in pre-term delivery.

Breast-feeding

A small amount of moclobemide is excreted in breast milk. The benefits of continuing therapy for a nursing mother should be weighed against the possible risks to the child.

No data on Fertility available.

4.7 Effects on ability to drive and use machines

Impairment of performance in activities that require complete mental alertness e.g. driving a car or operating machinery is generally expected with moclobemide therapy. However care should be taken with regard to these activities during initiation of therapy.

4.8 Undesirable effects

Moclobemide is usually well tolerated. Adverse effects reported during clinical trials include:

- Nervous system disorders

Central and Peripheral Nervous System

Incidences >1%: headache, pressure in head, insomnia, sleep disturbances, dizziness, tremor, increased agitation, restlessness, nervousness, sleepiness, somnolence, tiredness, sedation, increased anxiety, acute anxiety state, weakness or faintness.

Incidences <1%: migraine, extrapyramidal effects, tinnitus, paraesthesia, dysarthria, altered taste sensations

Anticholinergic

Incidence >1%: dry mouth

- Eye disorders

Incidences >1%: blurred vision

Incidences <1%: photopsia, visual disturbances

- Cardiac disorders

Cardiovascular

Incidences >1%: tachycardia, palpitations

Incidences <1%: bradycardia, extrasystoles, angina/chest pain, and dyspnoea

- Vascular disorders

Incidences >1%: hypotension, orthostatic reactive hypotension

Incidences <1%: hypertension, phlebitis symptoms, flushing

- Gastrointestinal disorders

Incidences >1%: nausea, constipation, gastrointestinal pain, epigastric discomfort, sickness, diarrhoea, abdominal fullness, abdominal pain, vomiting, and increase/loss of appetite

Incidences <1%: heartburn, gastritis, meteorism, indigestion.

- Skin disorders and subcutaneous tissue disorders

Dermatological/ Mucocutaneous:

Incidences <1%: exanthema/rash, allergic skin reaction, itching, gingivitis, stomatitis, dry skin, conjunctivitis, pruritus, urticaria.

- Musculoskeletal and connective tissue disorders

Incidences <1%: skeletal/muscular pain

- Renal and urinary disorders

Incidences <1%: disturbances of micturition (dysuria, polyuria, tenesmus) and metrorrhagia

- Reproductive system

Incidences <1%: prolonged menstruation, and hot flushes/cold sensation

- General disorders

Incidences < 1%: general malaise

Laboratory Abnormalities:

During clinical trials reductions were observed in leukocyte, AST and ALT values however these reductions were attributed to raised baseline values returning to normal and were not considered clinically relevant.

There appears to be a low incidence of raised liver enzymes without associated clinical sequelae.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

The usual signs of overdose with moclobemide alone are nausea, vomiting, drowsiness, disorientation, slurred speech, amnesia, reduced reflexes, agitation, hypertension and convulsions as well as QTc prolongation and Torsades de Pointes (TdP).

Combination overdoses of moclobemide and other antidepressants, alcohol, and other drugs can be life-threatening. Fatalities have been reported when moclobemide has been taken in combination with other drugs.

Patients should be hospitalised and closely monitored so that appropriate treatment can be given. Serotonin syndrome symptoms (hypertension, spasm, and altered consciousness) have been reported with mixed overdoses with clomipramine.

Treatment

Treatment should consist of general supportive measures. Gastric lavage or induction of emesis, activated charcoal and fluid control may be of benefit. Management of the overdose should include monitoring of vital signs and ECG monitoring as well as consideration of other agents ingested in multiple overdoses.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Psychoanaleptics and antidepressants

ATC code: N06AG

Actions

Moclobemide is a benzamide derivative which is a reversible inhibitor of monoamine oxidase type A. It inhibits the deamination of serotonin, dopamine and noradrenaline which leads to increased extracellular concentrations of these neuronal transmitters which may account for its antidepressant activity. Moclobemide relieves symptoms such as dysphoria, lack of drive, inability to concentrate and exhaustion. These effects most often appear within the first week of therapy. Moclobemide also relieves symptoms related to social phobia.

Even though moclobemide has no sedative properties, the quality of sleep in most depressed patients improves within days, without impairing alertness

Short-term and long-term animal studies indicate low toxicity. No cardiac toxicity has been observed. There appears to be a low incidence of raised liver enzymes without associated clinical sequelae.

5.2 Pharmacokinetic properties

Absorption

After oral administration, moclobemide is completely absorbed from the gastrointestinal tract into the portal circulation. Peak plasma levels occur within one to two hours. Hepatic first-pass metabolism reduces the systemically available dose fraction (bioavailability) to approximately 55% after a single dose and 90% after multiple doses. Following multiple doses of moclobemide, peak plasma concentrations increase over the first week of therapy and then stabilise. When the daily dose is increased there is a greater-than-proportional increase in steady state concentrations.

Distribution

Because moclobemide is lipophilic it is extensively distributed in the body with an apparent volume of distribution (VSS) is about 1.2L/kg. Binding to plasma proteins, mainly albumin, is approximately 50%. The presence of food reduces the rate but not the extent of absorption. Insignificant amounts are excreted in breast milk.

Metabolism

Moclobemide is almost completely metabolised in the liver before it is eliminated from the body. Metabolism occurs largely via oxidative reactions on the morpholine moiety of the molecule.

The N-oxide metabolite has slight pharmacological activity but other active metabolites recovered in vitro or in animal experiments are present only at very low concentrations in the systemic circulation in man.

Moclobemide has been shown to be metabolised in part by the polymorphic isoenzymes CYP2C19 and CYP2D6. In genetically or drug induced (via metabolic inhibitors) poor metabolisers, metabolism of moclobemide may be affected.

Studies suggest that due to the presence of multiple alternative metabolic pathways these effects are of no clinical significance and it should not necessitate dosage modification.

Elimination

Moclobemide is rapidly eliminated from the body. Total clearance is approximately 20-50L/hours. The average elimination half-life during multiple dosing (300 b.i.d.) is about 3 hours, and ranges from 2 to 4 hours in most patients. Metabolites are excreted renally. While 95% of the administered dose is excreted in the urine less than 1% of a dose is excreted renally in unchanged form.

Renal insufficiency does not appreciably alter the pharmacokinetics of moclobemide except for an increase in absorption time. In elderly patients C_{max} and AUC values are higher than in younger subjects and clearance decreased. Dose adjustments are not necessary for these two groups of patients.

In patients with severe hepatic impairment plasma concentration and elimination half-life are significantly increased while the clearance is significantly decreased. The daily dose should be reduced to one-half or one-third to reach the usual plasma level.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apo-Moclobemide 150mg tablet contains the following excipients:

- Colloidal silicon dioxide
- Croscarmellose sodium
- Dextrates
- Magnesium stearate
- Carnauba wax
- Hypromellose
- Iron oxide yellow
- Macrogol 3350
- Polydextrose
- Titanium dioxide

Apo-Moclobemide 300mg tablet contains the following excipients:

- Colloidal silicon dioxide
- Croscarmellose sodium
- Magnesium stearate
- Methyl cellulose
- Microcrystalline cellulose
- Hyprolose
- Hypromellose
- Macrogol 8000
- Titanium dioxide.

6.2 Shelf life

24 months from date of manufacture

6.3 Special Precautions

Store at or below 25°C

Protect from heat, light and moisture.

6.4 Nature and contents of container

APO-MOCLOBEMIDE 150mg: PVC/Aclar/Al blisters containing 100 and 500 tablets

APO-MOCLOBEMIDE 300mg: PVC/Aclar/Al blisters containing 60 and 100 tablets

Not all pack sizes maybe marketed.

6.5 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Glenfield
AUCKLAND 0627

Telephone: (09) 444 2073

Fax: (09) 444 2951

E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

14 September 2000

10. DATE OF REVISION OF THE TEXT

17 May 2017

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new data sheet.
6.1	Additional information as per Medsafe requirements