Aurorix®

Moclobemide

Antidepressant

1 Description

1.1 Type of Dosage Form

Aurorix 150mg film-coated tablet is in good appearance, evenly film-coated, oval, cylindrical, biconvex, clean-edge, pale yellow imprinted “150” above the tablet and break-mark below tablet.

1.2 Qualitative and quantitative composition

Active ingredient: Moclobemide (150mg)
Excipients: described as per local requirements

2 Clinical Particulars

2.1 Therapeutic indications

- Treatment of depressive syndromes

2.2 Dosage and Administration

2.2.1 Standard Dosage

Depressive syndromes

The recommended dose range of moclobemide is 300 and 600 mg of moclobemide (equivalent of 2 to 4 film-coated tablets Aurorix 150). Usually, this dosage is given in two to three divided doses after the meal.

The initial dose is 300 mg of moclobemide per day (equivalent of 2 film-coated tablets Aurorix 150 mg). In patients with severe depression, this dose may be increased to 600 mg of moclobemide daily (equivalent of 4 film-coated tablets Aurorix 150).

However, the dose should not be raised until after the first week, as bioavailability increases during this period (see section 3.2.5 Pharmacokinetics in Special Populations).

Note:
The dose of moclobemide does not need to be specially adjusted in elderly patients or patients with reduced renal function.

When hepatic metabolism is severely impaired by hepatic disease or by a medicine that inhibits the activity of certain liver enzymes (microsomal mono- oxsygenase) – such as cimetidine-, the daily dose of moclobemideshould be reduced to half or one third to reach the usual plasma level (see section 3.2.5 and 2.4.2).

With appropriate caution, a patient can be switched from moclobemide to tricyclic or other antidepressants without observing any waiting period, i.e. from one day to the other.

When switching a patient from other antidepressants to moclobemide, a washout phase is recommended the duration of which depends on the half-life of the previously administered antidepressant.

As a general rule, a free interval of 14 days is recommended when switching a patient from an irreversible MAO inhibitor (such as phenetzine, tranylcypromine) to moclobemide.

After end of treatment with selective serotonin reuptake inhibitors (SSRIs) and before treatment with moclobemide is initiated, a washout phase lasting up to 4 to 5 times the half-life of the active substance and its metabolites is recommended.

When switching to moclobemide, the dose should not exceed 300 mg/day during the first week of treatment.

2.2.2 Special Dosage Instructions

The dose should be taken after a meal with some liquid.

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

There is no limit with regard to the duration of treatment.

2.3 Contraindications

Moclobemide is contraindicated

- In case of known hypersensitivity to moclobemide or to any of the excipients of the medicinal product;
- in an acute confusional state;
- in children, as clinical experience in this patient group is lacking;
- in combination with selegiline, triptans, pethidine, tramadol, bupropion and dextromethorphan, linezolid. (see section 2.4.2).

2.4 Warnings and Precautions

2.4.1 General

Suicide/Suicidal thoughts or clinical worsening

Depressive disorders are associated with an increased risk of suicidal thoughts, self harm and suicide (suicide – related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase when treatment is initiated.

Other psychiatric conditions for which moclobemide is prescribed can also be associated with an increased risk of suicide – related events. In addition, these conditions may occur together with depressive disorders (episodes of major depression). For this reason, the same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide behavior, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts. They should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

As with other antidepressants, treatment may exacerbate the schizophrenic symptoms of depressive patients with schizophrenic or schizoaffective psychoses. If possible, therapy with long-acting neuroleptics should be continued in such patients.

Generally during therapy with moclobemide, special dietary restrictions are not necessary. Since hypersensitivity to tyramine may exist in some patients, all patients should be advised to avoid the consumption of large amounts of tyramine-rich food.

Suicidality on Children and Adolescent

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Suicidal thoughts, self-harm and suicide (suicide-related events) are known be associated with the conditions for which moclobemide is prescribed, but a possible increase in the risk of such events in patients treated with antidepressants can not be excluded. Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. The indication(s) approved in paediatric for the particular drug should be clearly stated / included.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose adjustment. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber immediately if these symptoms present.

When treating patients with schizophrenic or schizoaffective psychoses, exacerbation of schizophrenic symptoms may occur. If somehow possible, treatment with long-term neuroleptics should be continued in these patients.

In pharmacological studies, moclobemide has shown a slight potential only for interactions with tyramine. In contrast to a therapy with irreversible monoaminoxidase inhibitors, the interactions occurring with tyramine rich food under treatment with moclobemide are clinically insignificant under normal conditions and when the product is taken after the meals. However, as a precaution it is recommended that all patients avoid eating large amounts of tyramine rich food (such as old mature cheese).

In predisposed patients, hypersensitivity reactions manifesting themselves in symptoms including rash, oedema or dyspnoe may occur.

There are theoretical pharmacological grounds for supposing that drugs that inhibit monoamine oxidase may provoke hypertensive reaction in patients with thyrotoxicosis or pheochromocytoma. As experience with moclobemide in this population group is lacking, caution should be exercised with regard to prescribing moclobemide.

In patients receiving moclobemide, additional drugs that enhance serotonin, such as many other antidepressants, particularly in multiple-drug combinations, should be given with caution. Due to the increased risk of serious undesirable effects, concomitant administration of moclobemide and clomipramine should be avoided (see section 2.4.2).

Concomitant administration of moclobemide and buprenorphine containing products may result in serotonin syndrome, a potentially life-threatening condition (see section 2.4.2).

If concomitant treatment with other serotonergic agents is clinically warranted, careful

observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Concomitant administration of moclobemide and dextromethorphan (may be contained in medicines used to treat colds, for instance), is not recommended (see section 2.4.2).

Particular caution should be exercised when moclobemide is co-administered with herbal products containing St. John's wort (Hypericum) as this may increase the serotonin serum concentration.

Insomnia or nervousness or jitteriness at the beginning of treatment with moclobemide can justify a dose reduction or temporary symptomatic treatment. In case of occurrence of mania or hypomania, or the onset of early symptoms of those reactions (grandiosity, hyperactivity (including increased speech), reckless impulsivity), treatment with moclobemide shall be interrupted and alternative treatment should be initiated.

Excipient information

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take moclobemide.

2.4.2 Interaction with other medicinal products and other forms of interaction

Co-administration of moclobemide with selegiline or with lenezolid is contraindicated.

Co-administration of moclobemidewith triptans is contraindicated because they are potent serotonin receptor agonists and metabolized by monoamine oxidases (MAOs) and various cytochrome P450 enzymes thus increasing the plasma concentrations of the triptans (such as sumatriptan, rizatriptan, zolmitriptan, almotriptan, naratriptan, frovatriptan and eletriptan).

Co-administration of moclobemidewith tramadol is contraindicated.

In animals, moclobemide potentiates the effects of opiates. Concomitant use of moclobemide and opioids/opiate products (e.g., buprenorphine, buprenorphine containing products) may result in serotonin syndrome, a potentially life-threatening condition (see section 2.4.1). A dosage adjustment of the following products (e.g. morphine, fentanyl and codeine) may become necessary.

The combination with pethidine is contra-indicated because of the increased risk of serotonergic syndrome (confusion, fever, convulsions, ataxia, hyperreflexia, myoclonus, diarrhoea).

In pharmacological studies, moclobemide has shown minor potential only in respect of interactions with tyramine (see section 2.4.1). The potentiation of the pressor effect was even lower or did not occur when moclobemide was administered after a meal.

In order to obtain normal plasma levels, the daily dose of moclobemide should be reduced to half or one-third in patients who concomitantly use a medicinal product that

inhibits the activity of certain liver enzymes (microsomal mono-oxidase), such as cimetidine.(see section 2.2).

Care should be taken with concomitant use of medicinal products that are metabolised by CYP2C19 as moclobemide is an inhibitor of this enzyme. The plasma concentration of these drugs (such as proton pump inhibitors (e.g. omeprazole), fluoxetine and fluvoxamine) may be increased when concomitantly used with moclobemide.

Care should be taken with concomitant use of trimipramine and maprotiline as the plasma concentration of these monoamine reuptake inhibitors increases upon concomitant administration with moclobemide.

The pharmacologic action of systemic regimens of sympathomimetic agents may possibly be intensified and prolonged by concurrent treatment with moclobemide (e.g adrenergics).

In patients receiving moclobemide, additional drugs that enhance serotonin, such as many other antidepressants, particularly in multiple-drug combinations, should be given with caution. This applies in particular to anti-depressants such as venlafaxine, fluvoxamine, clomipramine, citalopram, escitalopram, paroxetine, sertraline, bupropion. In isolated cases, serious symptoms and signs, including hyperthermia, confusion, hyperreflexia and myoclonus, were reported which are indicative of serotonergic overactivity. Should such combined symptoms occur, the patient should be closely observed by a physician (and if necessary hospitalized) and appropriate treatment given.

Treatment with tricyclic or other antidepressant agents could be initiated the next day after withdrawal of moclobemide. When switching from other antidepressants to moclobemide, a washout phase is recommended the duration of which depends on the half-life of the previously administered antidepressants (see section 2.2.).

Concomitant use with St. John’s wort (Hypericum) products is not recommended as this may increase the serotonin serum concentration in the central nervous system.

Moclobemide must not be co-administered with dextromethorphan (may be contained in medicines used to treat colds, for instance)(see section 2.4.).

Data from clinical studies suggests that no interactions exist between moclobemide and hydrochlorothiazide (HCT), in hypertensive patients, with oral contraceptives, digoxin, phenprocoumon, and alcohol.

As sibutramine is a nor-epinephrine-serotonin reuptake inhibitor, which would increase the effect of MAOIs, the concomitant use with moclobemide is not recommended.

Concomitant use of dextropropoxyphene is not advised as moclobemide may potentiate the effects of dextropropoxyphene.

2.4.3 Effects on the ability to drive and use machines

In general, reactivity will not be impaired. The individual reaction should, however, be monitored in particular during early treatment.

2.5 Use in Special Populations

2.5.1 Fertility, pregnancy and lactation

Fertility
There are no adequate human data. Animal studies have not revealed any impairment of reproductive parameters.

Pregnancy
There are no adequate data from the use of this product in human pregnancy. Animal studies have not revealed risk to the fetus.

Breast-feeding
Only a small amount of moclobemide passes into the breast mild (approximately 1/30 of the body weight-corrected adult dose).
Therefore, the expected benefits of treatment with moclobemide during pregnancy and lactation should be weighed carefully against the possible risks.

2.6 Undesirable effects

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

Very Common (≥ 1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effect
Metabolism and nutrition disorders	Rare	Loss of appetite* Hyponatraemia*
Psychiatric disorders	Very common	Sleep disorders
	Common	Agitation, anxiety, restlessness
	Uncommon	Suicidal ideation Confusional state (these have resolved quickly on discontinuation of therapy)
	Rare	Suicidal behaviors, delusion*
Nervous system disorders	Very common	Dizziness, headache
	Common	Paraesthesia
	Uncommon	Dysgeusia
	Rare	Serotonin syndrome* (co-administered with drugs that enhance serotonin, such as serotonin re-uptake inhibitors and many other antidepressants, buprenorphine and buprenorphine containing products)
Eye disorders	Uncommon	Visual impairment
Vascular disorders	Common	Hypotension
	Uncommon	Flushing
Gastrointestinal disorders	Very common	Dry mouth, nausea
	Common	Vomiting, diarrhoea, constipation
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Oedema, pruritus, urticaria
General disorders	Common	Irritability
	Uncommon	Asthenia
Investigations	Rare	Increased hepatic enzymes
	Not known	Elevated plasma prolactin level

*: Adverse reactions that were not reported in clinical studies but were only reported post-marketing are indicated by an asterix (*)

When treating patients with schizophrenic or schizoaffective psychoses, exacerbation of schizophrenic symptoms may occur. If somehow possible, treatment with long-term neuroleptics should be continued in these patients (refer to section 4.4 “Special Warnings and Special Precautions for Use”).

Patients with suicidal tendencies should receive careful monitoring during the initial phase of treatment.

2.7 Overdose and Treatment

Symptoms of overdose

Overdoses of moclobemide alone induce generally mild and reversible signs of central nervous system disorders and gastro-intestinal irritation.

Mixed overdoses of moclobemide with other drugs (e.g. other CNS-acting substances) – depending on their toxicity - could be life-threatening. Therefore, these patients should be hospitalized and closely monitored.

Treatment of overdose

Treatment of overdose should primarily be aimed on maintaining the vital functions.

3 PHARMACOLOGICAL PROPERTIES

3.1 Pharmacodynamic properties

3.1.1 Mechanism of Action

Moclobemide is an antidepressant which affects the monoaminergic cerebral neurotransmitter system by means of a reversible inhibition of monoamine oxidase preferentially of type A (RMAO-A). The metabolism of noradrenaline, dopamine and serotonin is decreased by this effect, and this leads to increased extracellular concentrations of these neuronal transmitters.

As a result of its elevating effect on mood and psychomotor activity, moclobemide relieves symptoms such as dysphoria, exhaustion, lack of drive and inability to concentrate. These effects most often appear within the first week of therapy. Moclobemide also relieves symptoms related to social phobia.

Though moclobemide has no sedative properties, it improves the quality of sleep in most depressive patients within days. Moclobemide does not impair alertness.

3.1.2 Clinical / Efficacy Studies

Short-term and long-term animal studies indicate low toxicity. No cardiac toxicity has been observed.

3.2 Pharmacokinetic properties

3.2.1 Absorption

After oral administration, moclobemide is completely absorbed from the gastrointestinal tract into the portal blood. Peak plasma concentrations of the drug are usually reached within one hour of administration. A hepatic first-pass effect reduces the systemically available dose fraction (bioavailability). However, saturation of these metabolic pathways during the first week of dosing (300-600 mg/day) results in essentially complete oral bioavailability thereafter. Plasma concentrations following multiple doses of moclobemide

increase over the first week of therapy and then stabilize. When the daily dose is increased, there is a greater-than-proportional increase in steady-state concentrations.

3.2.2 Distribution

Due to its lipophilic nature, moclobemide is extensively distributed in the body. The volume of distribution (V_{SS}) is about 1.0 l/kg. Binding of the drug to plasma proteins, mainly albumin, is low (50%). Insignificant amounts are excreted in human breast milk.

3.2.3 Biotransformation

The drug is almost entirely metabolised before its elimination from the body. Metabolism occurs largely via oxidative reactions on the morpholine moiety of the molecule. Degradation products with pharmacological activity are present in the systemic circulation in man at very low concentrations only. The major metabolites present in plasma are a lactam derivative and an N-oxide derivative. Moclobemide has been shown to be metabolised in part by the polymorphic isoenzymes CYP2C19 and CYP2D6. Thus, in genetically or drug-induced (via metabolic inhibitors) poor metabolisers, metabolism of the drug may be affected. Two studies conducted to investigate the magnitude of these effects suggested that, due to the presence of multiple alternative metabolic pathways, they are of no clinical significance and should not necessitate dosage modification.

3.2.4 Elimination

Moclobemide is rapidly eliminated by metabolic processes. Total clearance is approximately 20 – 50 l/hour. The mean elimination half-life during multiple dosing (300 mg b.i.d) is approximately 3 hours and generally ranges from 2 – 4 hours in most patients. Less than 1% of a dose is excreted renally in unchanged form. The metabolites formed are eliminated renally. Insignificant amounts are secreted in human breast milk.

3.2.5 Pharmacokinetics in special populations

Elderly
Absorption and disposition parameters are unchanged in the elderly.

Patients with renal impairment
Renal disease does not alter the elimination characteristics of moclobemide.

Patients with hepatic impairment
In advanced liver insufficiency, the metabolism of moclobemide is reduced (see section 2.2).

4 PHARMACEUTICAL PARTICULARS

4.1 Storage

This medicine should not be used after the expiry date (EXP) shown on the pack. See also outer pack for storage remark.

4.2 Packs

Film-coated tablets (scored) 150mg packs to 30 and 100 tablets
Aurorix 150 mg film-coated tablets are packed in laminated blister foil.

Medicine: keep out of reach of children

Storage: Store at temperatures not exceeding 30°C

Manufacturer

Made for
MEDA Pharma GmbH & Co. KG,
Benzstrasse 1,
61352 Bad Homburg
Germany

by
Cenexi SAS
52, rue Marcel et Jacques
Gaucher 94120 Fontenay-sous-
Bois France

Date of Revision
Current at July 2023

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

MEDA Pharma GmbH & Co. KG,
Bad Homburg, Germany