Composition
Moclobemide 100 mg, 150 mg, and 300 mg; tablets.

Properties
Moclobemide is an antidepressant which affects the monoaminergic cerebral neurotransmitter system through reversible inhibition of monoamine oxidase, preferentially of type A. The metabolism of norepinephrine, dopamine and serotonin is thus decreased, and this leads to increased extracellular concentrations of these neuronal transmitters. As a result of its elevating effect on mood and psychomotor activity, Aurorix relieves symptoms such as dysphoria, exhaustion, lack of drive and inability to concentrate. The effects most often appear within the first week of therapy.

Though Aurorix has no sedative properties, it does improve the quality of sleep in depressive patients within days. Aurorix does not impair alertness. Short-term and long-term animal studies indicate low toxicity. No hepatic or cardiac toxicity has been observed.

Pharmacokinetics
Absorption
After oral administration, moclobemide is completely absorbed from the gastrointestinal tract into the portal circulation. A hepatic first-pass effect reduces the systemically available dose fraction (bioavailability [F]) in a dose-dependent manner (40-80%). This reduction is more pronounced after single (F: 60%) than after multiple (F: >80%) doses.

Distribution
Moclobemide is lipophilic. The apparent volume of distribution (Vss) is about 1.2 l/kg. Binding of the drug to plasma proteins, mainly albumin, is relatively low (50%). Peak plasma concentrations of the drug are reached within one hour of administration. 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 an over-proportional increase in steady-state concentrations.

Metabolism
The drug is almost entirely metabolized before being eliminated from the body. Metabolism occurs largely via oxidative reactions on the morpholine moiety of the molecule. Active metabolites recovered in vitro or in animal experiments are present only at very low concentrations in the systemic circulation in man. Approximately 2% of the Caucasian population and 15% of the Asian population can be genetically phenotyped as slow metabolizers with respect to oxidative hepatic metabolism. It was found that the mean area under the curve (AUC) in slow metabolizers is approximately 1.5 times greater than the same parameter measured in extensive metabolizers for the same dose of moclobemide. However, this increase is within the normal range of variation (up to 2-fold) typically seen across all patients.

Elimination
Moclobemide is rapidly eliminated from the body. Total clearance is approximately 20-50 l/hour. The elimination half-life is one to four hours. Less than 1% of a dose is excreted renally in unchanged form. Metabolites are likewise eliminated renally.

Indications
Treatment of depressive syndromes.

Contraindications
Known hypersensitivity to the drug. Acute confusional states.

Aurorix should not be used in pediatrics at present, as clinical experience of the drug’s action in children is lacking.

Co-administration of moclobemide with selegiline (Deprenyl) is contraindicated.

Side Effects
The following side effects have been observed: sleep disturbances, agitation, feelings of anxiety,
irritability, dizziness, headache, paresthesia, dry mouth, visual disturbances, gastrointestinal complaints and skin reactions (such as rash, pruritus, urticaria and flushing). Some undesirable effects can be due to underlying symptoms of the illness and disappear in most cases with continuation of the therapy. Isolated cases of confusion have been seen; these have resolved quickly on discontinuation of therapy.

**Precautions**

As is usual in antidepressant therapy, patients with suicidal tendencies should be closely monitored. 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. There are theoretical pharmacological grounds for supposing that monoamine oxidase inhibitors may provoke hypertensive reactions in patients with thyrotoxicosis or pheochromocytoma. In the absence of relevant experience with moclobemide, the drug should be prescribed with caution to patients in these groups.

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. Impairment of performance in activities requiring complete mental alertness (e.g. driving a motor vehicle) is generally not to be expected with Aurorix. The individual reaction, however, should be monitored during early treatment.

In patients receiving moclobemide, the additional use of other drugs that enhance serotonin, such as many other antidepressants, particularly in multiple drug combinations, should be done with caution. This is particularly true for clomipramine. This is because in isolated cases there have been a combination of serious symptoms and signs, including hyperthermia, confusion, hyperreflexia and myoclonus, which are indicative of serotonergic overactivity. Should such combined symptoms occur, then the patient should be closely observed by a physician (if necessary hospitalized) and appropriate treatment given.

Isolated cases of severe, central nervous system adverse reactions have been reported after co-administration of moclobemide and dextromethorphan. Since cough and cold medicines may contain dextromethorphan, they should not be taken without prior consultation with the physician, such that non-dextromethorphan-containing alternatives may be given. Hypersensitivity may occur in susceptible individuals. Symptoms may include rash and edema.

**Pregnancy, Nursing Mothers**

Reproduction studies in animals have not revealed any risk to the fetus, but the safety of Aurorix in human pregnancy has not been established. Therefore the benefits of the drug therapy during pregnancy should be weighed against possible risks to the fetus. Although only a small amount of moclobemide passes into breast milk (approx. 1/30 of the maternal dose when correcting for body weight differences), the benefits of continuing drug therapy for a nursing mother should be weighed against possible risks to the child.

**Overdosage**

Mono-overdoses of moclobemide induce generally mild and reversible signs of CNS and gastrointestinal irritation which do not need particular intervention. Treatment should be aimed at support of vital functions. As with other antidepressants, mixed overdoses with moclobemide (e.g. with other CNS-acting drugs) could be life-threatening. Therefore, patients should be hospitalized and closely monitored so that appropriate treatment may be given.

**Stability**

This medicine should not be used after the expiry date (EXP) shown on the pack.

**Drug Interactions**

In animals, moclobemide potentiates the effects of opiates. Dosages of these drugs therefore may have to be adjusted. The combination with pethidine is not recommended.
Cimetidine prolongs the metabolism of moclobemide. The usual dosage of Aurorix should therefore be approximately halved in patients taking cimetidine.

Treatment with a tricyclic or other antidepressant could be initiated immediately after withdrawal of Aurorix, i.e. without a wash-out period and vice versa. When switching to moclobemide, the dose should not exceed 300 mg/day during the first week. The pharmacologic action of systemic regimens of sympathomimetic agents may possibly be intensified and prolonged by concurrent treatment with moclobemide.

Because the action of Aurorix is selective and reversible, its propensity to interact with tyramine is slight and short-lasting as pharmacological studies in animals and man have shown (see Precautions). The potentiation of the pressor effect was even lower or did not occur when moclobemide was administered after a meal.

**Dosage and Administration**

The recommended dose range of moclobemide is 300-600 mg daily usually administered in two to three divided doses. The initial dose is 300 mg daily and may be increased to 600 mg/day for severe depression.

Dosages should not be raised until after the first week, as bioavailability increases during this period (see Pharmacokinetics). The dose should be taken after a meal. The individual response may allow a reduction of the daily dose.

**Special Dosage Instructions**

Aurorix dosage 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 a drug (e.g. cimetidine) that inhibits microsomal monooxygenase activity, normal plasma levels are achieved by reducing the daily dose of Aurorix to half or one third.