

AURORIX



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## 1. Product Name

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Aurorix 150 mg and 300 mg film coated tablets.

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## 2. Qualitative and Quantitative Composition

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Each tablet contains 150 mg or 300 mg of moclobemide.

Aurorix tablets contain lactose. For the full list of excipients, see section 6.1.

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## 3. Pharmaceutical Form

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Aurorix 150 mg: Oval, cylindrical, biconvex, pale yellow film coated tablet marked "150" on one side with a break mark on the other side. Tablets are about 15 mm by 8 mm.

Aurorox 300 mg: Oval, cylindrical, biconvex, white to yellowish-white film coated tablet marked "300" on one side with a break mark on the other side. Tablets are about 15mm by 8mm.

The tablets can be divided into equal doses.

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## 4. Clinical Particulars

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### 4.1 *Therapeutic indications*

Aurorix is indicated for the treatment of depressive syndromes and social phobia.

### 4.2 *Dose and method of administration*

#### **Dose**

#### ***Depressive syndromes***

The recommended dose range of Aurorix is 300 - 600 mg daily. Treatment with moclobemide can begin with the full therapeutic dose of 300 - 450 mg in 2 or 3 oral divided doses after meals. The dose may be increased to 600 mg/day for severe depression.

The dose should not be raised until after the first week, as bioavailability increases during this period (see section 5.2).

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

#### ***Social phobia***

The recommended dose of Aurorix is 600 mg/day, given in 2 divided doses. Treatment with 600 mg/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 responding patient. Results of long-term studies indicate that the efficacy of treatment with Aurorix is maintained with continued use. Patients should be re-evaluated periodically to determine need for further treatment.

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Patients can be switched to moclobemide from other antidepressants and vice versa without a washout period. When switching to Aurorix, the dose should not exceed 300 mg/day during the first week (see section 4.5).

### ***Special populations***

#### **Elderly**

Elderly patients do not require a special dose adjustment of Aurorix.

#### **Renal impairment**

Patients with reduced renal function do not require a special dose adjustment.

#### **Hepatic impairment**

When hepatic metabolism is severely impaired by hepatic disease or inhibited by a medicine that inhibits microsomal mixed function oxidase activity (e.g. cimetidine), the daily dose of Aurorix should be reduced to half or one third (see sections 4.5 and 5.2).

#### **Paediatric**

In view of a lack of clinical data, Aurorix is not recommended for use in children.

### **Method of administration**

The dose should be taken after a meal.

## **4.3 Contraindications**

Patients with known hypersensitivity to moclobemide or to any of the excipients listed in section 6.1.

Acute confusional states.

Co-administration of Aurorix with the following medicines is contraindicated (see also section 4.5):

- selegiline
- bupropion
- triptans
- pethidine
- tramadol
- dextromethorphan
- linezolid.

Aurorix should not be used in paediatrics, as clinical experience of the medicine's action in children is lacking.

## **4.4 Special warnings and precautions for use**

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.

Hypersensitivity may occur in susceptible individuals. Symptoms may include rash and oedema.

Theoretical pharmacological considerations indicate that MAO inhibitors may precipitate a 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 Aurorix, 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 (see section 4.5).

Co-administration of moclobemide and dextromethorphan, which may be contained in cough cold medicines, is not recommended (see section 4.5).

St. John's wort (hypericum) containing phytotherapeutic products should be used with care in combination with moclobemide as this may increase serotonin concentration.

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

### **Suicide / suicidal thoughts or clinical worsening**

Depression is 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 in the early stages of recovery.

Other psychiatric conditions for which Aurorix is prescribed can also be associated with an increased risk of suicide – related events. In addition, these conditions may be co-morbid with major depressive disorder. 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 – related events, 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, and 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.

Close supervision of patients, and in particular those at high risk, should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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 will be interrupted and alternative treatment will be initiated.

### **4.5 Interaction with other medicines and other forms of interaction**

Co-administration of Aurorix with selegiline or with linezolid is contraindicated.

Co-administration of Aurorix with triptans is contraindicated, because they are potent serotonin receptor agonists and metabolized by monoamine oxidases (MAOs) and various cytochrome P450 enzymes and the plasma concentrations of the triptans increases, e.g. sumatriptan, rizatriptan, zolmitriptan, almotriptan, naratriptan, frovatriptan and eletriptan.

Co-administration of Aurorix with tramadol is contraindicated.

In animals, moclobemide potentiates the effects of opiates. A dosage adjustment of the following opiates e.g. morphine, fentanyl and codeine may therefore be necessary for these medicines.

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

Since 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 section 4.4).

The potentiation of the pressor effect was even lower or did not occur when moclobemide was administered after a meal.

The daily dose of moclobemide should be reduced to half or one-third in patients whose hepatic metabolism is severely inhibited by a drug that blocks microsomal mixed function oxidase activity, such as cimetidine (see section 4.2).

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 (such as proton pump inhibitors (e.g. omeprazole), fluoxetine and fluvoxamine) may be increased when concomitantly used with moclobemide. Similarly, moclobemide inhibits the metabolism of omeprazole in CYP2C19 extensive metabolisers resulting in a doubling of the omeprazole exposure.

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 Aurorix, additional medicines that enhance serotonin, such as many other antidepressants, particularly in multiple combinations, should be given with caution. This is particularly true for antidepressants such as venlafaxine, fluvoxamine, clomipramine, citalopram, escitalopram, paroxetine, sertraline, bupropion. This is because in isolated cases there has 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, the patient should be closely observed by a physician (and if necessary hospitalized) and appropriate treatment given. Treatment with a tricyclic or other antidepressant could be initiated the next day after withdrawal of moclobemide. When switching from a serotonin reuptake inhibitor to Aurorix, the half-life of the former should be taken into account (see section 4.4). Generally, an interval of 14 days is recommended when switching from an irreversible MAO inhibitor to moclobemide (e.g. phenelzine, tranylcypromine).

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

Isolated cases of severe central nervous system adverse reactions have been reported after co-administration of Aurorix and dextromethorphan. Since cough and cold medicines may contain dextromethorphan, they should not be taken without prior consultation with the physician, and if possible, alternatives not containing dextromethorphan should be given (see section 4.4).

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 norepinephrine-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.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

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

### Breast-feeding

Although only a small amount of moclobemide passes into breast milk (approx. 1/30 of the maternal dose), the benefits of continuing therapy during breast-feeding should be weighed against possible risks to the child.

### Fertility

No data available.

## 4.7 Effects on ability to drive and use machines

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 should however be monitored during early treatment.

## 4.8 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 ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

<b>Metabolism and nutrition disorders</b>	
Rare	Decreased appetite* Hyponatraemia*
<b>Psychiatric disorders</b>	
Very common	Sleep disorder
Common	Agitation, anxiety, restlessness
Uncommon	Suicidal ideation Confusional state (these have resolved quickly on discontinuation of therapy)
Rare	Suicidal behaviours, delusion*
<b>Nervous system disorders</b>	
Very common	Dizziness, headache
Common	Paraesthesia
Uncommon	Dysgeusia
<b>Eye disorders</b>	
Uncommon	Visual impairment
<b>Vascular disorders</b>	
Common	Hypotension
Uncommon	Flushing

<b>Gastrointestinal disorders</b>	
Very common	Dry mouth, nausea
Common	Vomiting, diarrhoea, constipation
<b>Skin and subcutaneous tissue disorders</b>	
Common	Rash
Uncommon	Oedema, pruritus, urticaria
<b>General disorders and administration site conditions</b>	
Common	Irritability
Uncommon	Asthenia
<b>Investigations</b>	
Rare	Serotonin syndrome* (co-administered with drugs that enhance serotonin, such as serotonin re-uptake inhibitors and many other antidepressants) Increased hepatic enzymes (without associated clinical sequelae)

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

### 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

Overdoses of moclobemide alone induce generally mild and reversible signs of CNS and gastrointestinal irritation. Treatment should be aimed at support of vital functions.

As with other antidepressants, mixed overdoses of moclobemide with other medicines (e.g. with other CNS-acting medicines) could be life-threatening. Therefore, patients should be hospitalized and closely monitored so that appropriate treatment may be given.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

## 5. Pharmacological Properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressant, ATC code: N06 AG02

Aurix is an antidepressant which affects the brain monoaminergic neurotransmitter system by means of a reversible inhibition of monoamine oxidase, preferentially of type A (RMAO-A). The metabolism of norepinephrine, 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, Aurix relieves symptoms such as dysphoria, exhaustion, lack of drive and inability to concentrate. These effects most often appear within the first week of therapy. Aurix also relieves symptoms related to social phobia.

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

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

## **5.2 Pharmacokinetic properties**

### **Absorption**

After oral administration, moclobemide is completely absorbed from the gastrointestinal tract into the portal blood. Peak plasma concentrations of moclobemide 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.

### **Distribution**

Due to its lipophilic nature, moclobemide is extensively distributed in the body. The volume of distribution ( $V_{ss}$ ) is about 1.01/kg.

Binding of the medicine to plasma proteins, mainly albumin, is low (50%).

### **Metabolism**

Moclobemide 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 moclobemide may be affected. Two studies conducted to investigate the magnitude of these effects suggested that, due to the presence of multiple alternative metabolic pathways, in general they are of no clinical significance and should not necessitate dosage modification (see section 4.2).

### **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 twice daily) 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.

### **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 4.2).

## **5.3 Preclinical safety data**

Preclinical data, based on conventional studies of safety pharmacology, single and repeat dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction did not reveal special hazards for humans associated with moclobemide.

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## 6. Pharmaceutical Particulars

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### 6.1 *List of excipients*

Tablet core: Lactose, maize starch, polyvidone, sodium starch glycollate, magnesium stearate.

Film coat: Methylhydroxypropylcellulose, ethylcellulose, polyethylene glycol, talc and titanium dioxide (E171); and yellow iron oxide (E172) in 150 mg tablets only.

Aurorix tablets contain lactose and are gluten free.

### 6.2 *Incompatibilities*

Not applicable.

### 6.3 *Shelf life*

5 years

### 6.4 *Special precautions for storage*

Store at or below 30°C.

### 6.5 *Nature and contents of container*

Blister packs of 100 and 60 tablets (150 mg)

Blister packs of 60 tablets (300 mg)

Not all pack sizes may be marketed.

### 6.6 *Special precautions for disposal and other handling*

Not applicable.

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## 7. Medicines Schedule

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Prescription Medicine

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## 8. Sponsor Details

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Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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## 9. Date of First Approval

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21 June 1991 (Aurorix 150 mg)

30 June 1994 (Aurorix 300 mg)

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## 10. Date of Revision of the Text

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13 April 2018

Change in tablet descriptions (Section 3).

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