SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AURORIX® 300 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet

Active substance:

Moclobemide	300.00 mg

Excipients:

Lactose	26.50 mg
Sodium starch glycolate	25.00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Oval, cylindrical, biconvex, white to yellowish-white colored, odorless, scored on one side and engraved with DEVA 300 on the other side film coated tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Indicated for the treatment of major depressive and social phobia.

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Unless otherwise recommended by the physician;

Major depression:

The recommended dosage range for moclobemide is 300-600 mg/day, administered in two or three divided doses generally. The starting dose is 300 mg per day and can be increased up to 600 mg/day in severe depression. The dose should not be increased until after the first week of treatment, as bioavailability increases during this period (see section

5.2 Pharmacokinetic properties). To assess efficacy, treatment should be continued for at least 4–6 weeks.

Social Phobia:

The recommended dose of AURORIX is 600 mg/day in two divided doses. Treatment should be started with 300 mg/day and increased to 600 mg/day on the 4th day. To determine the effectiveness of the drug, treatment with a dose of 600 mg/day should be continued for 8-12 weeks. Social phobia can be a chronic condition, and therefore, continuing treatment may be appropriate in patients who respond. Results of long-term studies suggest that the effectiveness of AURORIX is maintained with long-term treatment. Patients should be re-evaluated at regular intervals to determine the need for further treatment.

Method of administration:

AURORIX tablets are to be taken orally.

Doses should be taken after meals.

Additional information for special populations

Renal/Hepatic impairment:

No special dosage adjustment of moclobemide is required in patients with reduced renal function, but should be used with caution.

If hepatic metabolism is severely impaired due to liver disease or inhibited by drugs such as cimetidine, the daily dose of moclobemide should be reduced to one-half or one-third. (See 4.4 Special warnings and precautions for use).

Pediatric population: AURORIX should not be used in pediatrics because there is insufficient clinical experience on the effect of the drug in children.

Geriatric population: No special dosage adjustment of moclobemide is required in the elderly.

4.3. Contraindications

- Use in patients with known hypersensitivity to moclobemide or any component of the drug
- Acute confusional states.

* AURORIX should not be used in pediatrics because there is insufficient clinical experience on the effect of the drug in children.
* Concomitant use of Selegiline and AURORIX is contraindicated. (See 4.5 Interactions with other medicinal products and other forms of interaction)
* Should not be used with sympathomimetics.
* Should not be used concomitantly with serotonergic medicines including MAO inhibitors, TCAs, meperidine, thioridazine, dextromethorphan, and SSRIs.

4.4. Special warnings and precautions for use

• As with other antidepressants, when used in depressive patients with schizophrenic or schizoaffective psychosis, an increase in schizophrenic symptoms may be observed. In such patients, treatment should, if possible, be continued with long-acting neuroleptics.

• In general, no specific dietary restrictions are required during AURORIX treatment. Since some patients may exhibit hypersensitivity to tyramine, all patients should be advised to avoid excessive consumption of tyramine-rich foods.

• Suicidal thoughts, self-harm and attempted suicide (suicide-like events) are known to be associated with situations for which AURORIX is recommended, but an increased risk of such events in patients treated with antidepressants cannot be excluded.

• As is known in antidepressant treatment, patients with suicidal tendencies should be carefully monitored.

• Depression is associated with an increased risk of suicidal thoughts and self-harm and suicidal behaviors (suicide-related events). This risk will last until significant remission occurs. Because this improvement may not be achieved within the first few weeks or longer of treatment, patients should be carefully monitored until improvement is observed. Clinical experience suggests that the risk of suicide may increase during the early stages of recovery.

• Other psychiatric conditions for which AURORIX is prescribed may also be associated with an increased risk of suicide-related events. These conditions may also co-exist with major depressive disorder. Therefore, the same precautions applied when treating patients with major depression should be observed when treating patients with other psychiatric disorders.

• Patients with a history of suicide-related events or significant suicidal ideation prior

to initiating treatment should be carefully monitored during treatment because they are at greater risk of suicidal thoughts or suicide attempts. A meta-analysis of placebo-controlled clinical trials of antidepressant use in adult psychiatric disorders has shown an increased risk of suicidal behavior in patients under the age of 25 treated with antidepressants compared to placebo. Patients at high risk, in particular, should be closely monitored following dose changes in the early stages of treatment.

- Hypersensitivity reactions may occur in susceptible individuals. Rash and edema may be seen as symptoms.
- Theoretical pharmacological considerations suggest that MAO inhibitors may trigger hypertensive crises in patients with thyrotoxicosis or pheochromocytoma. Since experience with moclobemide in this patient group is limited, caution should be exercised when deciding to use moclobemide.
- Hyponatremia may develop, usually in elderly patients, and possibly due to inappropriate antidiuretic hormone secretion.
- In patients using AURORIX, caution is advised against the development of serotonin syndrome, especially when other serotonin-enhancing drugs are used concurrently, particularly in repeated drug combinations. This is particularly relevant for clomipramine (See section 4.5 Interactions with other medicinal products and other forms of interaction).
- Moclobemide should not be used in combination with dextromethorphan, which may be present in cough and cold medications (See section 4.5 Interactions with other medicinal products and other forms of interaction).

Use with caution in patients who are overly excited or agitated.

May trigger manic episodes in patients with bipolar disorder.

The use of antidepressants, particularly in children and young adults up to the age of 24, may increase the risk of suicidal ideation or behavior. For this reason, the patient should be closely monitored by both the family and the treating physician, especially at the beginning and first months of treatment, and during periods when the drug dose is increased/decreased or discontinued, for unexpected behavioral changes such as restlessness, hyperactivity, or the possibility of suicide. Since clinical experience regarding the effects of the drug in children is insufficient, AURORIX should not be used in pediatrics.

Each AURORIX tablet contains 148.00 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
This medicinal product contains sodium. This situation should be taken into consideration for patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

- Concomitant use of AURORIX with selegiline is contraindicated.
- Moclobemide may potentiate the effects of opioids. Therefore, dosage adjustments of these medicines may be necessary. Its use in combination with pethidine is not recommended.
- Due to the selective and reversible effect of AURORIX, the possibility of interaction with tyramine is low and pharmacological studies have proven that the interaction is short-lived (See 4.4 Special warnings and precautions for use). When moclobemide is taken after meals, the potentiation of pressor effects is minimal or absent.
- Cimetidine prolongs the metabolism of moclobemide (See section 4.2 Posology and method of administration).
- The pharmacological effects of sympathomimetic agents may be potentiated and prolonged when administered concomitantly with systemically administered moclobemide. In patients taking AURORIX concurrently with other serotonin-enhancing agents, particularly in repeated combination therapies, caution should be exercised. This is especially important with clomipramine. The most important reason for this is that in isolated cases, a combination of signs and symptoms indicating serotonergic hyperactivity, such as hyperthermia, confusion, hyperreflexia and myoclonus, has been encountered. If such combined symptoms occur, the patient should be closely monitored by a physician (hospitalization may be necessary), and appropriate treatment should be initiated.
- Treatment with a tricyclic or other antidepressant may begin immediately after discontinuation of AURORIX, and vice versa, similar precautions should be followed. When restarting AURORIX treatment, the dose should not exceed 300 mg/day during the first week (See section 4.2 Posology and method of administration).

- Isolated cases of serious central nervous system reactions have been reported following concomitant use of AURORIX with dextromethorphan. Since cough and cold medicines may contain dextromethorphan, these medicines should not be used without consulting a doctor and, if possible, dextromethorphan-free medicines should be preferred (See 4.4 Special warnings and precautions for use).
- Carbamazepine: Due to the lack of interaction data, concomitant use is not recommended.
- Interactions may occur at the central level with acetylcholinesterase inhibitors.
- It is not recommended to take with alcohol.
- There may be interactions with herbal products (ginkgo, etc.).

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: B

Women of childbearing potential / Birth Control (Contraception)

There are no clinical data available on the exposure to moclobemide during pregnancy.

Animal studies do not indicate any direct or indirect harmful effects on pregnancy, embryonic/fetal development/parturition or postnatal development.

Pregnancy

There is not adequate information about its safety during pregnancy. Therefore, the potential benefit of treatment should be carefully weighed against any potential risks to the fetus.

Caution should be exercised when given to pregnant women.

Lactation

Although moclobemide passes into breast milk in very small amounts (approximately 1/30 of the maternal dose when correcting for differences in body weight), the benefits of continued treatment for the nursing mother should be considered against any possible risks to the infant.

4.7. Effects on the ability to drive and use machines

Performance impairment is not generally expected with AURORIX in activities requiring full mental alertness (e.g., driving motor vehicles). However, as with the initiation of any

treatment, extra caution should be exercised during the early phase of treatment when engaging in such activities.

4.8. Undesirable effects

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 available data).

Metabolism and nutrition disorders

Very rare: Hyponatremia

Psychiatric disorders

Unknown: Sleep disorders, agitation, anxiety. Isolated cases of confusion have been occurred, these resolved rapidly after stopping treatment.

Nervous system disorders

Unknown: Dizziness, headache, paresthesia, tremor

Eye disorders

Unknown: Visual disturbances

Cardiac disorders

Unknown: Tachycardia, hypotension

Vascular disorders

Unknown: Flushing, edema

Gastrointestinal disorders

Unknown: Dry mouth, gastrointestinal complaints

Skin and subcutaneous tissue disorders

Unknown: Skin reactions such as redness, itching, urticaria

General disorders and administration site conditions

Unknown: Irritability

Investigations

Unknown: There is an increase in liver enzymes, which is not associated with clinical sequelae and has a low incidence.

Some undesirable effects occur depending on the symptoms of the disease and in most cases disappear during the treatment period.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose and treatment

Moclobemide overdose alone usually results in mild and reversible CNS symptoms and gastrointestinal irritation. Treatment should be based on supporting vital functions. As with other antidepressants, multiple drug overdosage (e.g., with other CNS-active drugs) can be life-threatening for moclobemide. Therefore, these cases require hospitalization and close monitoring to ensure appropriate treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective, reversible MAO (Type-A) inhibitors (RIMAs)

ATC code: N06AG02

Moclobemide is an antidepressant that acts on the brain monoaminergic neurotransmitter system by selectively reversibly inhibiting monoamine oxidase A (RIMA). As a result of this effect, the metabolism of norepinephrine, dopamine and serotonin slows down and this situation increases the extracellular concentration of neuronal transmitters. As a result of its mood-enhancing and psychomotor activity-increasing effects, AURORIX is effective in alleviating symptoms such as dysphoria, fatigue, loss of desire to live, and reduced ability to concentrate. These effects usually appear within the first week of treatment. AURORIX also alleviates symptoms related to social phobia. Although AURORIX has no sedative properties, it improves sleep quality in most depressed patients within a few days. AURORIX does not disturb attention. No cardiac toxicity has been observed.

5.2 Pharmacokinetic properties

General characteristics

Absorption: Moclobemide is completely absorbed from the gastrointestinal tract after oral administration. Peak plasma concentrations are usually reached within one hour. First-pass metabolism in the liver reduces the systemically available fraction of the drug (bioavailability) in a dose-dependent manner. However, during the first week of

administration (300-600 mg/day), metabolic pathways become saturated, resulting in complete oral bioavailability. Following repeated doses of moclobemide, plasma concentrations increase during the first week of treatment and then stabilize. When the daily dose is increased, the rise in steady-state concentrations is higher than would be expected from a proportional increase in dose.

Distribution: Moclobemide is lipophilic. Volume of distribution (V_{ss}) is approximately 1.0 L/kg. Plasma protein binding is low (around 50%), mainly to albumin. Transfer into breast milk is minimal.

Biotransformation: The drug is almost completely metabolized before excretion. Metabolism mainly occurs through oxidative reactions on similar parts of the morpholine molecule. Active metabolites have been found in very low concentrations in the systemic circulation. The primary metabolites found in plasma are lactam and N-oxide derivatives. It has been shown that moclobemide is partially metabolized by the polymorphic isoenzymes CYP2C19 and CYP2D6. Therefore, in individuals with metabolic deficiencies due to genetic factors or drug use (e.g., metabolic inhibitors), the metabolism of the drug may be affected. However, in two studies conducted to determine the significance of these effects, it was shown that, due to the presence of multiple alternative metabolic pathways, these effects are therapeutically insignificant and do not require dose adjustments.

Elimination: Moclobemide is rapidly eliminated via metabolism. Total clearance is approximately 20–50 L/hour. With repeated dosing (300 mg bid), the average elimination half-life is approximately 3 hours and varies between 2 and 4 hours in most patients. Less than 1% of the dose is excreted unchanged via the kidneys. Metabolites are also excreted via the kidneys in a similar manner.

Linearity/Non-linearity: Up to doses of 200 mg, the pharmacokinetics of moclobemide exhibit linear characteristics. At higher doses, however, non-linear pharmacokinetics have been observed. In the 400–1200 mg dose range, maximum plasma concentrations increase, and clearance decreases in a manner disproportionate to the dose.

Characteristics in patients

Elderly patients: In elderly individuals, absorption and distribution parameters do not change.

Patients with impaired renal function: Renal insufficiency does not affect the elimination characteristics of moclobemide.

Patients with impaired liver function: In advanced liver failure, the metabolism of moclobemide is reduced.

5.3. Preclinical safety data

None reported.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core:

Lactose

Maize Starch

Povidone

Sodium Starch Glycolate

Magnesium Stearate

Film coating:

Hydroxypropyl methylcellulose

Ethylcellulose dispersion

Polyethylene glycol 6000

Talc

Titanium dioxide (E171)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

60 months.

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

AURORIX 300 mg film-coated tablets, 30 pieces, in blister

6.6. Special precautions for disposal and other handling

Unused products or waste material should be disposed of in accordance with the "Regulation on the Control of Medical Wastes" and the "Regulation on the Control of Packaging and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

220/67

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorization: 02.09.2009
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT