Core Safety Profile

Active substance: Moclobemide
Pharmaceutical form(s)/strength: Tablets 150 and 300 mg
P-RMS: NL/H/PSUR/0031/002
Date of FAR: 10.12.2013
4.3 Contraindications

Patients with known hypersensitivity to moclobemide or to any component of the product. Acute confusional states. 
\( ... \) should not be used in pediatrics at present, as clinical experience of the drug's action in children is lacking.

Co-administration of \( ... \) with the following drugs is contraindicated (see also section 4.5 Interaction with other medicinal products and other forms of interaction):

- Selegiline
- Linezolid
- Triptans
- Pethidine
- Tramadol
- Bupropion
- Dextromethorphan

4.4 Special warnings and special precautions for use

Warnings

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 edema.

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 moclobemide, additional drugs that enhance serotonin such as many other antidepressants, particularly in multiple-drug combinations, should be given with caution. This is particularly true for clomipramine, (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Co-administration of moclobemide and dextromethorphan, which may be contained in cough cold medicines, is not recommended (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

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

Precautions

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 /.../ 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 behavior 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 behavior or thoughts and unusual changes in behavior 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 medicinal products and other forms of interaction

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

Co-administration of /.../ 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 /.../ 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.

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

Since the action of /.../ 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 Special warnings and precautions for use).

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 Posology and method of administration).

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 /.../, additional drugs that enhance serotonin, such as many other antidepressants, particularly in multiple-drug combinations, should be given with caution. This is particularly true for anti-depressants 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 moclobemide, the half-life of the former should be taken into account (see section 4.4. Special warnings and precautions for use). Generally, an interval of 14 days is recommended for 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 /.../ 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. Special warnings and precautions for use).

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 not recommended.

Concomitant use of dextropropoxyphene is not advised as moclobemide may potentiate the effects of dextropropoxyphene.
4.6 Pregnancy and lactation

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

Lactation
Since only a small amount of /.../ passes into breast milk (approximately 1/30 of the maternal dose), the benefits of continuing drug therapy during nursing should be weighed against possible risks to the child.

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 /.../. 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 (≥ 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)

Metabolism and nutrition disorders:
Rare: Decreased appetite*
Rare: Hyponatraemia*

Psychiatric disorders:
Very common: Sleep disorder
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

**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 and administration site conditions:**
Common: Irritability
Uncommon: Asthenia

**Investigations:**
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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.
4.9 Overdose

Signs
Overdoses of moclobemide alone induce generally mild and reversible signs of CNS and gastro-intestinal irritation.

Management
Treatment of overdose should be aimed primarily at maintenance of the vital functions.

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