SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Moclobemide 300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of moclobemide.

Excipients with known effect:

Each film-coated tablet contains 36.05 mg of lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, oval, with score line on both sides
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Moclobemide is indicated for the treatment of major depressive episodes.

4.2 Posology and method of administration

Adults:
Initial usual dose 300 mg, administered in divided doses after meals. The tablets are for oral administration and should be taken with fluid.

If necessary, the daily dose can be increased to 600 mg per day. However, the dose should not be increased during the 1st week of treatment, because the

bioavailability increases during this time and a clinical effect may not be seen for 1-3 weeks. In individual cases, the therapeutic dose can be gradually reduced to 150 mg per day, depending on effect.

Duration of treatment:
Treatment with moclobemide should be continued for at least 4-6 weeks to be able to judge the efficacy of moclobemide. Treatment with moclobemide should preferably be continued for a symptom free period of 4-6 months. Then treatment can be gradually tapered off.

Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Elderly:
No special dose adjustment is required

Paediatric population:
In view of the lack of clinical data available, moclobemide is not recommended for use in children and adolescents under the age of 18.

Renal/hepatic impairment:
Patients with reduced renal function do not require a special dose adjustment. In patients with impaired hepatic function, the daily dose of moclobemide should be reduced to a half or one third.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute confusional states.
- Patients with phaeochromocytoma.
- Moclobemide 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 the following drugs is contraindicated (see also section 4.5):
    - Selegiline
    - Linezolid
    - Triptans
    - Pethidine
    - Tramadol
    - Bupropion
    - Dextromethorphan
    - 5-HT re-uptake inhibitors or other antidepressants (including tricyclic antidepressants)

4.4 Special warnings and 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 tricyclic antidepressants (e.g. clomipramine), selective serotonin (5-HT) re-uptake inhibitors (SSRI), other antidepressants or amphetamines (see section 4.3 and 4.5). A wash-out period is required between SSRIs and moclobemide therapy (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 the serotonin concentration.

Moclobemide contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol (23 mg) sodium per film-coated tablet, that is to say essentially 'sodium-free'.

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 Moclobemide 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.

Depressive patients with excitation or agitation as the predominant clinical symptoms should either not be treated with moclobemide or only in combination with a sedative for not more than 2-3 weeks. If a depressive episode is treated in bipolar disorders, manic episodes may be provoked, in such cases treatment with moclobemide should be stopped.

Patients with hypertension should be closely monitored when being treated with moclobemide. Patients should be advised to avoid sympathomimetic agents, such as ephedrine, pseudoephedrine and phenylpropanolamine (contained in many proprietary cough medicinal products).

Patients should also be advised that if they require surgery they should inform the anaesthesiologist that they take moclobemide.

Caution should be exercised in patients with congenital long QT syndrome or with a history of cardiac disorders (including disturbances of conduction, arrhythmia).

Concomitant administration of QT prolonging medicinal products should be avoided.

Serotonin syndrome

Concomitant administration of Moclobemide and buprenorphine or buprenorphine/ naloxone may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with buprenorphine or buprenorphine/naloxone 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Co-administration of Moclobemide 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 Moclobemide 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 Moclobemide 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 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 anti-depressants such as venlafaxine, fluoxetine, 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, rigidity, hyperreflexia, myoclonus, tachycardia and rise in blood pressure, 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). The starting dose of moclobemide should not exceed 300 mg daily during the first week.
Generally, an interval of 14 days is recommended for switching from an irreversible MAO inhibitor to moclobemide (e.g. phenelzin, 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 Moclobemide 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 not recommended.

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

The pharmacological effect of systemically administered sympathomimetics (epinephrine and norepinephrine) may be potentiated and prolonged during treatment with moclobemide, a dosage adjustment may therefore be necessary for these active substances.

At the present time, there is no experience of concomitant administration of moclobemide and buspirone in humans. However, cases of hypertensive crisis have been reported when other MAOIs were administered simultaneously with buspirone, therefore concurrent administration of buspirone and moclobemide is not recommended.

The combination with other medicinal products that are known to prolong the QT interval should be avoided. Moclobemide should not be given with class Ia and III antiarrhythmics, cisapride, macrolide antibiotics, antihistamines, medicinal products, known to cause hypokalemia (e.g. certain diuretics) or can inhibit the hepatic degradation of moclobemide (e.g. cimetidine, fluoxetine).

Moclobemide should be used cautiously when co-administered with:

Buprenorphine and buprenorphine/naloxone as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

4.6 Fertility, pregnancy and lactation

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

Breastfeeding
Since only a small amount of moclobemide 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

No studies on the effect on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The undesirable effects observed during treatment with moclobemide are observed mainly during the first few weeks of treatment and regress subsequently, concomitantly with improvement of the depressive episode. This is particularly so for some of the undesirable effects that are related to the very nature of the depressive illness such as feelings of anxiety, agitation or irritability, mood switch with mania or delirium.

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 (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data).

Metabolism and nutrition disorders
Rare: decreased 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

Eye disorders
Uncommon: visual impairment

Cardiac disorders
Moclobemide can cause QT interval prolongation. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia.

Vascular disorders:
Common: hypotension
Uncommon: flushing

Gastrointestinal disorders
Very common: nausea, dry mouth
Common: diarrhoea, constipation, vomiting

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: oedema, pruritus, urticaria

Reproductive system and breast disorders
Very rare: galactorrhea

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 Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

4.9 Overdose

Signs
Experience of overdose in humans is so far limited. Overdoses of moclobemide alone induce generally mild and reversible signs of CNS and gastro-intestinal irritation. Signs of agitation, aggressiveness, and behavioral changes have been observed. Although moclobemide alone, even in high doses, seldom leads to fatal reactions, death due to overdose of moclobemide as the only drug has been reported.

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.
Moclobemide prolongs the QT and QTc intervals in overdose and a 12-lead ECG should be done in the case of moclobemide overdose.
Therefore, patients should be hospitalised and closely monitored so that appropriate treatment may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant

ATC code: N06 AG 02

Moclobemide is an antidepressant that acts on the monoaminergic cerebral neurotransmitter system by reversibly inhibiting monoamine oxidase, primarily type A (RIMA). The metabolism of noradrenaline, dopamine and serotonin is thereby reduced, resulting in increased extracellular concentrations of these neurotransmitters.

5.2 Pharmacokinetic properties

After oral administration, moclobemide is absorbed completely from the gastrointestinal tract into the portal vein. A first-pass effect in the liver reduces the systemically available dose fraction (bioavailability F). This reduction is more pronounced after a single dose (F: 60%) than after multiple doses (F: 80%). Due to its lipophilic properties, moclobemide is distributed in the body with a volume of distribution (Vss) of approx. 1.2 l/kg. Binding to plasma proteins, mainly albumin, is relatively low (50%). Peak plasma concentrations are reached within 1 hour after administration. After multiple doses, the plasma concentrations of moclobemide increase over the first week of therapy, and thereafter remain stable. When the daily dose is increased, the increase in steady-state concentrations is more than proportional.

Moclobemide is almost entirely metabolised before it is eliminated: less than 1% of a dose is excreted unchanged via the kidneys. Metabolism occurs mainly via oxidative reactions in the morpholine part of the molecule. The metabolites formed are excreted renally. Degradation products with pharmacological activity *in vitro* or in animal studies occur only in very low concentrations in humans.

Plasma clearance is approximately 20-50 l/hour, and the elimination half-life is 1 - 4 hours, this increases with higher doses due to saturation of the metabolic pathways.

Approximately 2% of the Caucasian population and 15% of the Asian population have been shown to be slow metabolisers with respect to oxidative hepatic metabolism via the cytochrome P450 2C19 isozyme. The maximum plasma concentration (C_{max}) and the area under the concentration time curve (AUC) have been found to be approximately 1.5 times greater in slow metabolisers compared with extensive metabolisers for the same dose of moclobemide.

5.3 Preclinical safety data

Preclinical data, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction indicate there are no special hazards for humans associated with moclobemide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Povidone

Lactose monohydrate

Magnesium stearate (Ph.Eur.)

Maize starch

Microcrystalline cellulose

Sodium starch glycollate (type A) (Ph.Eur.)

Silica colloidal anhydrous.

Coating:

Lactose monohydrate

Hypromellose

Macrogol 4000

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/Alu blisters and inserted in a carton.

Pack sizes:

20, 30, 50, 60, 100 film-coated tablets (For hospital use only: 50 film-coated tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1420

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2007

10 DATE OF REVISION OF THE TEXT

06/10/2023