SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Moclobemide 150mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 150mg moclobemide.
Excipient with known effect: Each tablet contains 156.6 mg lactose (anhydrous).

For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Moclobemide- ratiopharm 150mg :Yellow, coated, oval, biconvex shaped tablets with a white core, scored on one side and imprinted "P" logo "150" on the other side.

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 300mg, administered in divided doses after meals. The tablets should be taken with fluid.

If necessary, the daily dose can be increased to 600mg 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 150mg, 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Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.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.

Patients with renal or 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 paediatrics 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 section 4.5):
  - Selegiline
  - 5-HT re-uptake inhibitors and other antidepressants (including those which are trycyclic antidepressants)
  - Linezolid
  - Triptans
  - Pethidine
  - Tramadol
  - Bupropion
  - Dextromethorphan

4.4 Special warnings and precautions for use
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.

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.

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.

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.

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 (e.g. mature cheese or red wine).

Hypersensitivity may occur in susceptible individuals. Symptoms may include rash and oedema. Although no interaction with alcohol has been demonstrated, it is recommended to avoid alcohol, as with any psychotropic medication.

Patients with hypertension should be closely monitored when being treated with moclobemide. Theoretical pharmacological considerations indicate that MAO inhibitors may precipitate a hypertensive reaction in patients with
thyreotoxicosis. As experience in this patient group is lacking, caution should be exercised with regard to prescribing 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.

In patients receiving moclobemide, additional drugs that enhance serotonin, such as many other antidepressants, particularly in multiple-drug combinations, should be given with caution in order to prevent precipitation of serotonergic syndrome. This is particularly true for clomipramine and selective serotonin (5-HT) re-uptake inhibitors (SSRI) antidepressants (see sections 4.3 and 4.5). A wash-out period is required between SSRIs and moclobemide therapy (see section 4.5).

Moclobemide should be used with care in patients with known risks for QT prolongation (e.g. patients with congenital LQTS, bradycardia and/or hypokalemia) as QT-prolongation might occur in this population. Caution is also advised if moclobemide is used together with medicines known to prolong the QTc interval.

Co-administration of moclobemide and dextromethorphan, which may be contained in cough cold medicines, is contraindicated (see sections 4.3 and 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 is not recommended for children (see section 4.3).

In the case of liver dysfunction, the dose should be reduced (see section 4.2). Moclobemide-ratiopharm 150mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of moclobemide with selegiline, tramadol or linezolid is contraindicated (see section 4.3).

Co-administration of moclobemide with triptans is contraindicated, because they are potent serotonin receptor agonists and metabolized by monoamine oxidases (MAOIs) and various cytochrome P450 enzymes and the plasma concentrations of the triptans increases, e.g. sumatriptan, rizatriptan, zolmitriptan, almotriptan, naratriptan, frovatriptan and eletriptan (see section 4.3).
Co-administration of moclobemide with dextromethorphan is contraindicated (see section 4.3). 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, alternatives not containing dextromethorphan have to be given (see sections 4.3 and 4.4).

In animals, moclobemide potentiates the effects of opiates (e.g. pethidine, dextromethorphan and tramadol, see section 4.3). A dosage adjustment of the following opiates e.g. morphine, fentanyl and codeine may therefore be necessary.

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

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 antidepressants such as tricyclic antidepressants, 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, hyperreflexia, rigidity, irritability, tachycardia, rise in blood pressure and myoclonus, which are indicative of serotonergic overactivity (serotonin syndrome). Combination treatment has caused deaths (see sections 4.3 and 4.4). Should such combined symptoms occur, the patient should be closely observed by a physician (and if necessary hospitalized) and appropriate treatment given.

Switching from another antidepressant agent to moclobemide: a wash-out period is recommended depending on the half-life of the antidepressant agent. Due to the generally long half-lives of SSRIs, a wash-out period of 4-5 half-lives of the active substance or any active metabolite is recommended after stopping treatment with the SSRI and starting treatment with moclobemide.

Generally, an interval of 14 days is recommended for switching from an irreversible MAO inhibitor (e.g. phenelzin, tranylcypromine) to moclobemide. When switching to moclobemide, the dose should not exceed 300 mg/day during the first week (see section 4.4).

Treatment with tricyclic, MAOIs or other antidepressant could be initiated the next day after withdrawal of moclobemide.

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

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 (e.g. adrenergics) may possibly be intensified and prolonged by concurrent 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.

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 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 (approx. 1/30 of the maternal dose), the benefits of continued 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 taking into consideration the adverse events profile. 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.

The frequencies of adverse events are ranked according to the following: 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).

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>very common</th>
<th>common</th>
<th>uncommon</th>
<th>rare</th>
<th>very rare</th>
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<tbody>
<tr>
<td></td>
<td>decreased appetite*, hyponatraemia*</td>
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<thead>
<tr>
<th>Psychiatric disorders</th>
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<th>common</th>
<th>uncommon</th>
<th>rare</th>
<th>very rare</th>
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</thead>
<tbody>
<tr>
<td>Sleep disorder</td>
<td>agitation, anxiety, restlessness</td>
<td>suicidal ideation, confusional state (these have resolved quickly on discontinuation of therapy)</td>
<td>suicidal behaviours, delusion*</td>
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<tr>
<th>Nervous system</th>
<th>very common</th>
<th>common</th>
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<td>dizziness, headache</td>
<td>paraesthesia</td>
<td>dysguesia</td>
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<tr>
<td>Disorders</td>
<td>Visual impairment</td>
<td>Hypotension flushing</td>
<td>Dry mouth, nausea</td>
<td>Vomiting, diarrhoea, constipation</td>
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<td>Vascular disorders</td>
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<td>Investigations</td>
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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 at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Signs
Overdoses of moclobemide alone induce generally mild and reversible signs of CNS and gastro-intestinal irritation. Signs of agitation, aggressiveness, and behavioural changes have been observed. Moclobemide prolongs the QT and QTc intervals in overdose and 12-lead ECG should be done on moclobemide overdoses.

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.

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. In rats, moclobemide and its metabolites were found in the amniotic fluid indicating that moclobemide is crossing the placental barrier.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

* Moclobemide-ratiopharm 150 mg *

Lactose, anhydrous
Maize starch
Sodium starch glycollate (type A)
Povidone
Magnesium stearate.

Tablet coat:

* Moclobemide-ratiopharm 150 mg *

Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Glyceryl triacetate
Ferric oxide yellow (E172).
6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

HDPE bottle and PVC/alu blister

Packsizes:
150mg: 10, 20, 28, 30, 40, 50, 60, 84, 90, 100, 100 x 1, 500 (10 x 50 as hospital pack only) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Straße 3
D-89079 Ulm
Germany
8 MARKETING AUTHORISATION NUMBER(S)
PL 15773/0075

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/09/2002

10 DATE OF REVISION OF THE TEXT
02/07/2014