Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Manerix 150 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg moclobemide.
Each tablet contains 140.6 mg of lactose monohydrate.
For a full list excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets
Oblong pale yellow tablet with '150' printed on one face, scored on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of moderate or severe depression.

4.2 Posology and method of administration

Adults
The initial daily dose is 300mg -usually in two or three divided doses. The effects should usually occur within two to three weeks. If this response is inadequate the dose may be increased to a maximum of 600mg daily. Depending on response the dosage may be reduced slowly to as low as 150mg daily after four weeks. If no response occurs, treatment should be discontinued.

The dose should not be raised until after the first week, as bioavailability increased during this period. Treatment should continue for at least 4-6 weeks in order to assess the efficacy of the drug.

It is generally recommended that treatment should be continued until the patient has been free of symptoms for four to six months and then gradually tapered off.

Elderly
Older people do not require a special dose adjustment of Manerix.

Paediatric Population
In view of the lack of clinical data available, Manerix is not recommended for use in the paediatric population.

Renal impairment
Patients with reduced renal function do not require a special dose adjustment of Manerix.

Hepatic impairment
When hepatic metabolism is severely impaired by hepatic disease or a drug that inhibits microsomal mono-oxygenase activity (e.g. cimetidine), normal plasma levels are achieved by reducing the daily dose of Manerix to half or one third (see section 4.5 Interaction with other medicinal products and other forms of interaction and section 5.2 Pharmacological properties).

Method of administration

Manerix film-coated tablets are for oral administration. The dose should be taken after a meal.

4.3 Contraindications

- Manerix is contraindicated in patients with known hypersensitivity to moclobemide or any of the excipients listed in section 6.1.
- Manerix is contra-indicated in acute confusional states.
- Manerix should not be administered to paediatric populations, as clinical experience of the drug's action in paediatrics is lacking.
- Co-administration of Manerix with the following drugs is contraindicated (see also section 4.5 Interaction with other medicinal products and other forms of interaction).

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

4.4 Special warnings and precautions for use

Warnings
Generally during therapy with moclobemide, special dietary restrictions are not necessary. However, 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.

There have been rare reports of hypertension or aggravated hypertension in a few patients taking moclobemide.

Depressive patients with excitation or agitation as the predominant clinical feature should either not be treated with Manerix or only in combination with a sedative (e.g. a benzodiazepine) for not more than 2-3weeks.

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.

In patients receiving Manerix, caution should be exercised when co-administering drugs that enhance serotonin (such as SSRI's, clomipramine and many other antidepressants, particularly in multi-drug combinations) in order to prevent precipitation of the serotonin syndrome (See section 4.5 *Interactions with other medicaments and other forms of interaction).* Should symptoms suggestive of the serotonin syndrome occur, the patient should be closely observed by a physician (and if necessary hospitalized) and appropriate treatment given.

If a depressive episode is treated in bipolar disorders, manic episodes can be provoked.

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

Hyponatremia, (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants, although very rarely with Manerix (see 4.8 Undesirable Effects) and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

Due to the lack of clinical data, patients with concomitant schizophrenia or schizo-affective organic disorders should not be treated with Manerix.

Theoretical pharmacological considerations indicate that Monoamine Oxidase (MAO) inhibitors may precipitate a hypertensive reaction in patients with thyrotoxicosis or pheochromocytoma. As experience with Manerix in this population group is lacking, caution should be exercised before prescribing Manerix.

There is a possibility that a pharmacogenetic abnormality in mephenytoin metabolism may affect the metabolism of moclobemide. The clinical significance of this is unknown.
Hypersensitivity may occur in susceptible individuals. Symptoms may include rash and oedema.

Co-administration of moclobemide and dextromethorphan (which may be contained in cough and cold medicines) is not recommended (see section 4. 5 Interaction with other medicaments and other forms of interaction).

Theoretical considerations indicate that the product should only be used with caution in patients with epilepsy.

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

This medicine contains less than 1 mmol sodium (23 mg) per 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 Manerix 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 medicinal products and other forms of interactions

Co-administration of Manerix with selegiline or with linezolid is contraindicated.
Co-administration of Manerix 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 Manerix 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).

Because the action of moclobemide is selective and reversible, its propensity to interact with tyramine is slight and short-lasting (see section 4.4 above) as pharmacological studies in animals and man have shown. 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).

Treatment with tricyclic antidepressants can be initiated without a wash out period.

In patients receiving moclobemide, the additional use of other drugs that enhance serotonin, such as many other antidepressants, particularly in multiple-drug combinations, should be done with caution.

This is particularly true for -anti-depressants such as venlafaxine, fluvoxamine, clomipramine, citalopram, escitalopram, paroxetine, sertraline and bupropion. This is because in isolated cases there have been a combination of serious symptoms and signs, including hyperthermia, confusion, hyperreflexia and myoclonus, which are indicative of serotonergic overactivity (serotonin syndrome). Should such combined symptoms occur, then the patient should be closely observed by a physician (and if necessary hospitalised) and appropriate treatment given.

Treatment with a tricyclic or other antidepressant could be initiated the next day after withdrawal of moclobemide (i.e. without a wash-out period) and vice-versa, provided similar caution is observed.

When switching from a serotonin reuptake inhibitor to moclobemide, the half-life of the former should be taken into consideration (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. 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 Manerix 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).

The possibility exists that the pharmacological effect of sympathomimetic drugs systemically administered may be potentiated and prolonged during concomitant treatment with Manerix.
There is, to date, no experience with co-administration of moclobemide and buspirone in humans.

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 Manerix 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 moclobemide passes into breast milk (less than 0.06% of the adult 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

Manerix has generally no or negligible influence on the ability to drive and use machines. The individual reaction should however be monitored during early treatment.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:
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*, hyponatraemia* (see section *4.4 Special warnings and precautions for use).*

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 behaviours, delusion*

Nervous system disorders:
Very common: Dizziness, headache
Common: paraesthesia.
Uncommon: Dysgeusia
Rare: Serotonin syndrome* (co-administered with drugs that enhance serotonin, such as serotonin re-uptake inhibitors and many other antidepressants)

Eye disorders:
Uncommon: Visual impairment

Vascular disorders:
Common: Hypotension
Uncommon: Flushing.

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

Hepatobiliary disorders
Rare: Increased hepatic enzymes (without associated clinical sequelae)

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

General disorders and administration site conditions:
Common: Irritability.
Uncommon: Asthenia
*: 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidepressant, ATC code: N06 AG 02
Moclobemide is an antidepressant which affects the monoaminergic cerebral neurotransmitter system by means of a reversible inhibition of monoamine oxidase preferentially of type A (RIMA). The metabolism of noradrenaline, dopamine and serotonin (5-HT) is decreased by this effect, and this leads to increased extracellular concentrations of these neuronal transmitters. Short-term and long-term animal studies indicate low toxicity. No cardiac toxicity has been observed. There appears to be a low incidence of raised liver enzymes without associated clinical sequelae.

5.2 Pharmacokinetic properties

Absorption
After oral administration, moclobemide is completely absorbed from the gastrointestinal tract into the portal blood. Peak plasma concentrations of the drug 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 (VSS) is about 1.0 l/kg. Binding of the drug to plasma proteins, mainly albumin is relatively low (50%).

Metabolism
The drug is almost entirely metabolised before its elimination from the body. Metabolism occurs largely via oxidative reactions on the morpholine moiety of the molecule. The metabolites formed are eliminated renally. Degradation products with pharmacological activity in *in vitro* or animal experiments 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 the drug 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 Posology and method of administration).

Elimination
Moclobemide is rapidly eliminated from the body. Total clearance is approximately 20-50 l/hour, the elimination half-life one to two hours with a slight increase at increased doses.

The mean elimination half-life during multiple dosing (300 mg b.i.d) 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.

Pharmacokinetics in 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 Posology and method of administration).

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. Only a small amount of Manerix passes into breast milk (approximately 1/30 of the maternal dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose monohydrate
Maize starch
Povidone
Sodium starch glycollate (Type A)
Magnesium stearate

In the film coat
Hypromellose
Ethylcellulose
Macrogol 6000
Talc
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC blister packs with an aluminium cover foil.

Pack sizes: 28, 30, 84, and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

PA2010/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation 04 July 1991

Date of last renewal: 04 July 2006

10 DATE OF REVISION OF THE TEXT

February 2021