

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Manerix 300mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated 300mg tablet contains 300mg moclobemide.

3 PHARMACEUTICAL FORM

300mg of moclobemide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Major depression.

Treatment of social phobia.

4.2 Posology and method of administration

Manerix tablets are for oral administration.

The tablets should be taken at the end of a meal.

Adults Major depression

The recommended initial dose is 300mg daily, usually administered in 2-3 divided doses. The dose may be increased up to 600mg/day depending on the severity of the depression.

The individual response may allow a reduction of the daily dose to 150mg.

The dose should not be raised until after the first week, as bioavailability increases during this period.

Treatment should continue for at least 4-6 weeks in order to assess the efficacy of the drug.

Treatment of social phobia

The recommended dose of moclobemide is 600mg/day, given in 2 divided doses. The moclobemide dose should be started at 300mg/day and should be increased to 600mg/day on day 4. Continuing the 300mg/day dose for longer than 3 days is not recommended, as the efficacious dose is 600mg/day. Treatment with 600mg/day should continue for 8 - 12 weeks in order to assess the efficacy of the drug. Social phobia may be a chronic condition and it is reasonable to consider continuation of treatment for a responding patient. Patients should be periodically re-evaluated to determine need for further treatment.

Special populations

Elderly

Elderly patients do not require a special dose adjustment of Manerix.

Children

In view of the lack of clinical data available, Manerix is not recommended for use in children.

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 see section 5.2 *Pharmacological properties*).

4.3 Contraindications

Manerix is contra-indicated in patients with known hypersensitivity to the drug or to any component of the product, in acute confusional states and in patients with phaeochromocytoma.

Manerix should not be co-administered with the following drugs (see section

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

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

Manerix should not be co-administered with 5-HT re-uptake inhibitors (including those which are tricyclic antidepressants) in order to prevent precipitation of serotonergic overactivity (see section 4.4 *Special warnings and precautions for use*, section 4.5 *Interaction with other medicinal products and other forms of interaction* and section 4.8 *Undesirable effects*). After stopping treatment with 5-HT re-uptake inhibitors a time period equal to 4 - 5 half lives of the drug or any active metabolite should elapse between stopping therapy and starting therapy with Manerix.

Manerix should not be co-administered with dextromethorphan, contained in many proprietary cough medicines, as isolated cases of severe central nervous system adverse reactions have been reported after co-administration.

Manerix should not be administered to children for the time being as clinical experience in this category is lacking.

4.4. Special warnings and precautions for use

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.

Manerix is a reversible inhibitor of monoamine oxidase type A (RIMA). It causes less potentiation of tyramine than traditional irreversible MAOIs, and therefore Manerix does not generally necessitate the special dietary restrictions required for these irreversible MAOIs. However, as a few patients may be especially sensitive to tyramine, all patients should be advised to avoid the consumption of large amounts of tyramine rich food (mature cheese, yeast extracts and fermented soya bean products).

Patients should be advised to avoid sympathomimetic agents such as ephedrine, pseudoephedrine and phenylpropanolamine (contained in many proprietary cough and cold medications) (see section 4.5 *Interaction with other medicinal products and other forms of interaction*).

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). The sedative should only be used for a maximum of 2 to 3 weeks.

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

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

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

Serotonin syndrome

In patients receiving Manerix, caution should be exercised when co-administering drugs that enhance serotonin in order to prevent precipitation of serotonergic syndrome (see section

4.3 Contraindications and section *4.5 Interaction with other medicinal products and other forms of interaction*).

Concomitant administration of Manerix and buprenorphine may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with buprenorphine 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.

Hypersensitivity may occur in susceptible individuals. Symptoms may include rash and oedema.

Hyponatraemia, (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.

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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 comorbid 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.

Owing to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 Manerix with pethidine or selegiline is contraindicated (see section 4.3 *Contraindications*).

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, bupropion, dextromethorphan and linezolid are contraindicated.

In animals, Manerix potentiates the effects of opiates. Opiate analgesics, such as, Morphine, Codeine and fentanyl should be used with caution. A dosage adjustment may

be necessary for these drugs.

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

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.

In patients receiving Manerix, 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 and sertraline. In isolated cases there have been combinations of serious symptoms and signs, including hyperthermia, confusion, hyperreflexia and myoclonus, which are indicative of serotonergic overactivity (see section 4.3 Contraindications, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects). Should such combined symptoms occur, 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. When switching from a serotonin reuptake inhibitor to Manerix 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, tranlycypromine).

Manerix should be used cautiously when co-administered with buprenorphine as the risk of serotonin syndrome, a potentially life-threatening condition (see section 4.4).

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

The pharmacologic action of systemic regimens of sympathomimetic agents may possibly be intensified and prolonged by concurrent treatment with moclobemide.

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).

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 Manerix 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

This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive

- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called ‘statutory defence’) if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

The following undesirable effects have been observed:

Metabolism and nutrition disorders:

Rare: Decreased appetite*
 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 behaviours, 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 reuptake 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 hospitalised and closely monitored so that appropriate treatment may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N06 AG 02

Pharmacotherapeutic group: antidepressant

Manerix 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.

As a result of its elevating effect on mood and psychomotor activity, Manerix relieves symptoms such as dysphoria, exhaustion, lack of drive and inability to concentrate. These effects most often appear within the first week of therapy. Manerix also relieves symptoms related to social phobia.

Though Manerix has no sedative properties, it improves the quality of sleep in most depressive patients within days. Manerix does not impair alertness.

Short-term and long-term animal studies indicate low toxicity. No cardiac toxicity has been observed.

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 dosage. A hepatic first-pass effect reduces the systemically available dose fraction (bioavailability F). This reduction is more pronounced after single (F: 60%) than after multiple (F: 80%) doses. After multiple dosing, plasma concentrations of moclobemide increase over the first week of therapy and remain stable thereafter. When the daily dose is increased, there is a more than proportional increase in steady-state concentrations.

Distribution

Due to its lipophilic nature, moclobemide is extensively distributed in the body. The volume of distribution (V_{ss}) is about 1.0 l/kg. Binding of the drug to plasma proteins, mainly albumin, is 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. Degradation products with pharmacological activity 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 by metabolic processes. Total clearance is approximately 20 - 50 l/hour. The mean elimination half-life during multiple dosing (300mg 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 excreted 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, maize starch, povidone K30, sodium starch glycollate, magnesium stearate, hydroxypropyl methylcellulose, ethylcellulose, polyethylene glycol 6000, talc and titanium dioxide (E171).

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

Blister packing.

Pack sizes: 30 and 60 tablets (300mg tablets)

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Viatrix Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0131

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First approved 5 June 1994

10 DATE OF REVISION OF THE TEXT

11/03/2026