SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE

MYTRA 15, mirtazapine 15 mg (Film-coated tablet)

MYTRA 30, mirtazapine 30 mg (Film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MYTRA 15: Each film-coated tablet contains mirtazapine 15 mg.

MYTRA 30: Each film-coated tablet contains mirtazapine 30 mg.

Excipient with known effect:

MYTRA 15 contains sugar (lactose monohydrate 102 mg).

MYTRA 30 contains sugar (lactose monohydrate 204 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

MYTRA 15: Yellow, biconvex, capsule shaped, film-coated tablets with a score line in between '1' and '5' on one side and 'MI' debossed on the other side.

MYTRA 30: Reddish brown, biconvex, capsule shaped, film-coated tablets with a score line in between '3' and '0' on one side and 'MI' debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive illness.

4.2 Posology and method of administration

Posology

Tablets should be taken orally.

MYTRA should be given in an initial dose of 15 mg, which may be increased gradually according to clinical response. The usual effective dose lies within the range of 15 mg to 45 mg. Daily doses may be given as a single dose, preferably at bedtime, or in two (2) equally divided doses.

Changes in dose should be made at intervals of at least one (1) to two (2) weeks because of the long half-life. For treatment of acute depressive episodes, treatment should be continued for at least six (6) months. MYTRA should be withdrawn gradually to reduce the risk of withdrawal symptoms.

The clearance of mirtazapine may be decreased in elderly patients and in patients with renal or hepatic impairment. This should be taken into account when prescribing MYTRA to this category of patients.

4.3 Contraindications

Hypersensitivity to the active substance of MYTRA, mirtazapine or to any of the excipients included in MYTRA (see section 6.1).

Pregnancy and lactation, as there is insufficient clinical data available.

Children and adolescents under the age of 18 years (see section 4.4).

Concomitant monoamine oxidase inhibitors (MAOIs) or within 14 days of discontinuation thereof (see section 4.5).

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age

MYTRA should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.3). Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants, such as MYTRA, compared to those treated with placebo.

Bone marrow depression

Bone marrow depression, usually presenting as granulocytopenia or agranulocytosis, has been reported during treatment with MYTRA.

Patients should be advised to report any of the following symptoms during treatment: fever, sore throat, stomatitis, or other signs of infection. These may be signs of bone marrow depression (neutropenia, agranulocytosis). Treatment should be stopped and a blood count performed.

Jaundice

Treatment should be stopped if jaundice develops.

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 may persist 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 with MYTRA.

Clinical trials of antidepressants, such as MYTRA, in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants, such as MYTRA, compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany therapy with antidepressants, such as MYTRA, 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.

With regards to the chance of suicide, in particular at the beginning of treatment, only a limited number of MYTRA tablets should be given to a patient.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme, which can be life-threatening or fatal, have been reported in association with MYTRA treatment.

If signs and symptoms suggestive of these reactions appear, MYTRA should be withdrawn immediately.

If the patient has developed one of these reactions with the use of MYTRA, treatment with MYTRA must not be restarted in this patient at any time.

Careful dosing as well as regular and close monitoring is necessary in patients with:

Epilepsy and organic brain symptoms: MYTRA should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures, or where there is an increase in seizure frequency.

Hepatic impairment: Following a single 15 mg oral dose of mirtazapine as contained in MYTRA 15, the clearance of mirtazapine was approximately 35 % decreased in mild to moderate hepatically impaired patients, compared to subjects with normal hepatic function. The average plasma concentration of mirtazapine as contained in MYTRA was about 55 % increased.

Renal impairment: Following a 15 mg oral dose of mirtazapine as contained in MYTRA, in patients with moderate (10 mL/min ≤ creatinine clearance < 40 mL/min) and severe (creatinine clearance < 10 mL/min) renal impairment the clearance of mirtazapine was about 30 % and 50 % decreased respectively, compared to normal subjects. The average plasma concentration of mirtazapine was about 55 % and 115 % increased, respectively. No significant differences were found in patients with mild renal impairment (40 mL/min ≤ creatinine clearance < 80 mL/min) as compared to the control group.

Cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken, and concomitant medicines carefully administered.

Low blood pressure.

Diabetes mellitus: In patients with diabetes, antidepressants such as MYTRA may alter glycaemic control. Insulin and / or oral hypoglycaemic dosage may need to be adjusted and close monitoring is recommended.

The following should be taken into account:

Worsening psychotic symptoms can occur when MYTRA is administered to patients with schizophrenia or other psychotic disturbances; paranoid thoughts can be intensified.

When the depressive phase of bipolar disorder is being treated, it can transform into the manic phase. Patients with a history of mania / hypomania should be closely monitored. MYTRA should be discontinued in any patient entering a manic phase.

Post-marketing experience with mirtazapine as contained in MYTRA shows that abrupt termination of treatment after long term administration of MYTRA may result in withdrawal symptoms. The majority of withdrawal reactions are mild and self-limiting. Among the various reported withdrawal symptoms, dizziness, agitation, anxiety, headache and nausea were the most frequently reported. As advised in section 4.2 it is recommended to discontinue treatment with MYTRA gradually.

MYTRA has weak antimuscarinic activity, therefore caution should be exercised in patients with micturition disturbances like prostate hypertrophy and in patients with eye disorders such as closed-angle glaucoma and raised intra-ocular pressure.

Akathisia / psychomotor restlessness: The use of MYTRA has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and a need to move often, accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

The effect of mirtazapine, such as contained in MYTRA, on QTc interval was assessed in a randomised, placebo and moxifloxacin controlled clinical trial involving 54 healthy volunteers using exposure response analysis. This trial revealed that both 45 mg (therapeutic) and 75 mg (supratherapeutic) doses of mirtazapine did not affect the QTc interval to a clinically meaningful extent. During the post-marketing use of mirtazapine, cases of QT prolongation, Torsades de Pointes, ventricular tachycardia and sudden death, have been reported. The majority of reports occurred in association with overdose or in patients with other risk factors for QT prolongation, including concomitant use of QTc prolonging medicines (see section 4.5). Caution should be exercised when MYTRA is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QTc interval.

Hyponatraemia: Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported with the use of MYTRA. Caution should be exercised in patients at risk, such as elderly patients or patients concomitantly treated with medications known to cause hyponatraemia.

Serotonin syndrome: Interaction with serotonergic active substances: Serotonin syndrome may occur when MYTRA is used concomitantly with other serotonergic active substances (see section 4.5). Symptoms of

serotonin syndrome may be hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Elderly patients

Elderly patients are often more sensitive, especially with regards to the undesirable effects of antidepressants, including MYTRA. During clinical research with mirtazapine as contained in MYTRA, undesirable effects have not been reported more often in elderly patients than in other age groups.

Monoamine oxidase inhibitor (MAOI)

In patients receiving MYTRA in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued MYTRA and then are started on an MAOI, there have been reports of serious and sometimes fatal reactions e.g. including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures and mental status changes ranging from agitation to coma. MYTRA should not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI including linezolid (see sections 4.3 and 4.5).

Lactose

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

MAOI: MYTRA should not be used concomitantly with MAOIs, including linezolid or within two (2) weeks of discontinuing a MAOI (see section 4.3).

In the opposite way about two (2) weeks should pass before patients treated with MYTRA should be treated with MAOIs (see section 4.3).

Alcohol: MYTRA may potentiate the central nervous depressant action of alcohol and patients should therefore be advised to avoid alcohol.

Anxiolytics and Hypnotics: Use of MYTRA may potentiate the sedative effects of benzodiazepines and other sedatives (including antipsychotics, antihistamine H_1 antagonists, opioids). Caution should be taken when these medicines are prescribed together with MYTRA.

Co-administration with other serotonergic active substances (L-tryptophan, triptans, tramadol, linezolid, methylene blue, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, lithium and St. John's Wort - *Hypericum perforatum* - preparations) may lead to an incidence of serotonin associated effects (serotonin syndrome: see section 4.4). Caution should be advised, and a closer clinical monitoring is required when these active substances are combined with MYTRA.

Mirtazapine such as contained in MYTRA dosed at 30 mg once daily caused a small, but statistically significant increase in the international normalised ratio (INR) in subjects treated with warfarin. As at a higher dose of MYTRA a more pronounced effect cannot be excluded. It is advisable to monitor the INR in case of concomitant treatment of warfarin with MYTRA.

The risk of QT prolongation and / or ventricular dysrhythmias (e.g. Torsades de Pointes) may be increased with concomitant use of medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics) and in case of MYTRA overdose.

Pharmacokinetic interactions

Carbamazepine and phenytoin, CYP3A4 inducers, increased mirtazapine, as contained in MYTRA, clearance about two-fold, resulting in a decrease in average plasma mirtazapine concentration of 60 % and 45 %, respectively. When carbamazepine or any other inducer of hepatic metabolism (such as rifampicin) is added to MYTRA therapy, the MYTRA dose may have to be increased. If treatment with such medicinal product is discontinued, it may be necessary to reduce the MYTRA dose.

Co-administration of the potent CYP3A4 inhibitor ketoconazole increased the peak plasma levels and the AUC of mirtazapine, as contained in MYTRA, by approximately 40 % and 50 % respectively.

When cimetidine (weak inhibitor of CYP1A2, CYP2D6 and CYP3A4) is administered with MYTRA, the mean plasma concentration of mirtazapine may increase more than 50 %. Caution should be exercised, and the dose may have to be decreased when co-administering MYTRA with potent CYP3A4 inhibitors, HIV protease inhibitors, azole antifungals, erythromycin, cimetidine or nefazodone.

Interaction studies did not indicate any relevant pharmacokinetic effects on concurrent treatment of MYTRA with paroxetine, amitriptyline, risperidone or lithium.

4.6 Fertility, pregnancy and lactation

MYTRA is contraindicated in pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

MYTRA may decrease alertness, judgement, thinking and concentration. Therefore, operating machinery or driving a vehicle should be avoided during treatment.

4.8 Undesirable effects

General disorders and administration site conditions:

Less frequent: Asthenia, flu like syndrome, increased sweating, fatigue.

Nervous system disorders:

Frequent: Drowsiness or sedation, dizziness, somnolence, headache, tremor, lethargy, amnesia.

Less frequent: Mania, hallucinations, convulsions, epileptic seizures, vertigo, agitation, paraesthesia, restless legs syndrome, myoclonus.

Metabolism and nutrition disorders:

Frequent: An increase in appetite and weight gain.

Gastrointestinal disorders:

Frequent: Dry mouth, constipation, nausea, vomiting, diarrhoea.

Less frequent: Thirst, oral hypoaesthesia, pancreatitis.

The following side effect has been reported but the frequency is unknown: Bitter taste in mouth.

Vascular disorders:

Frequent: Orthostatic hypotension.

Less frequent: Oedema, peripheral oedema.

Skin and subcutaneous tissue disorders:

Frequent: Exanthema.

Hepatobiliary disorders:

Less frequent: Elevations in serum transaminase activities.

The following side effect has been reported but the frequency is unknown: Jaundice may occur.

Investigations:

The following side effect has been reported but the frequency is unknown: Increases in liver enzyme levels have been reported.

Blood and the lymphatic system disorders:

Less frequent: Reversible agranulocytosis.

The following side effects have been reported but the frequencies are unknown: Leucopoenia and granulocytopenia.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Arthralgia and myalgia, back pain.

Psychiatric disorders

Frequent: Abnormal dreams, confusion, anxiety, insomnia.

Less frequent: Nightmares, psychomotor restlessness (incl. akathisia, hyperkinesia), aggression.

Post-marketing side effects

The reported post-marketing adverse reactions of which the frequency is not known:

Blood and the lymphatic system disorders: Bone marrow depression (granulocytopenia, agranulocytosis, aplastic anaemia and thrombocytopenia), eosinophilia.

Metabolism and nutrition disorders: Hyponatraemia.

Psychiatric disorders: Suicidal ideation, suicidal behaviour, somnambulism.

Nervous system disorders: Convulsions (insults), serotonin syndrome, oral paraesthesia, dysarthria.

Gastrointestinal disorders: Mouth oedema, increased salivation.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, dermatitis bullous, erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS).

General disorders and administration site conditions: Generalised oedema, localised oedema.

Renal and urinary disorders: Urinary retention.

Investigations: Increased creatinine kinase.

Musculoskeletal and connective tissue disorders: Rhabdomyolysis.

Endocrine disorders: Inappropriate antidiuretic hormone secretion, hyperprolactinemia (and related symptoms galactorrhoea and gynaecomastia).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MYTRA 15 & MYTRA 30 is important. It allows continued monitoring of the benefit / risk balance of MYTRA. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific antidote for MYTRA.

Present experience concerning overdose with MYTRA alone indicates that symptoms are usually mild. Depression of the central nervous system with disorientation and prolonged sedation have been reported, together with tachycardia and mild hyper- or hypotension. However, there is a possibility of more serious outcomes (including fatalities) at dosages much higher than the therapeutic dose, especially with mixed overdoses. In these cases, QT prolongation and Torsade de Pointes have also been reported.

Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

ECG monitoring should be undertaken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (Antidepressants)

Mirtazapine is a tetracyclic antidepressant, belonging to the piperazino-azepine group of compounds. Mirtazapine is centrally acting as a pre-synaptic α2-antagonist, which increases the central noradrenergic and serotonergic neurotransmission. It limits the effectiveness of inhibitory α2-adrenergic heteroreceptors on serotonergic neurons as well as inhibitory α2-autoreceptors and 5-HT2A heteroreceptors on noradrenergic neurons, which enhances the release of both amines.

It has antagonistic effects at several post-synaptic serotonin receptor types (including 5-HT2A, 5-HT2C and 5HT3 receptors) and can produce gradual down regulation of 5-HT2A receptors. These several actions probably contribute to the antidepressant effect. Mirtazapine also is a histamine H1-receptor antagonist, and correspondingly, relatively sedating.

5.2 Pharmacokinetic properties

Mirtazapine is well absorbed (bioavailability ~ 50 %), from the gastrointestinal tract with peak plasma levels occurring after about two (2) hours. Plasma protein binding is about 85 %. Mirtazapine is extensively metabolised in the liver and the major bio-transformation pathways are demethylation and oxidation followed by glucuronide conjugation; cytochrome P450 isoenzymes involved are CYP2D6, CYP1A2, and CYP3A4. The N-desmethyl metabolite is pharmacologically active. The mean plasma elimination half-life is 20 – 40 hours. Elimination is via urine (75 %) and faeces (15 %). Mirtazapine displays linear pharmacokinetics within the recommended dose range.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Hydroxypropyl cellulose

Maize starch

Silica, colloidal anhydrous (Aerosil 200)

Low-substituted hydroxypropyl cellulose (Grade LH-11)

Magnesium stearate

Film-coating:

MYTRA 15: Opadry Yellow 20A52560 consisting of:

Hydroxypropyl cellulose

Hypromellose

Titanium dioxide

Iron oxide yellow

MYTRA 30: Opadry Brown 20A56788 consisting of:

Hydroxypropyl cellulose

Hypromellose

Titanium dioxide

Iron oxide yellow

Iron oxide red

Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Four (4) years

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Store blisters in the original carton until required for use.

6.5 Nature and contents of container

Tablets are packed in white opaque PVC(250 μm) coated with PVdC (60 gm^2) as the forming material and aluminium foil (25 μm) as the lidding material, in the following pack sizes:

MYTRA 15: 30's

MYTRA 30: 30's

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd.

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene - Pretoria

8. REGISTRATION NUMBER(S)

MYTRA 15: A40/1.2/0652

MYTRA 30: A40/1.2/0653

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 October 2007

10. DATE OF REVISION OF THE TEXT

27 August 2021