Applicant: Oethmaan Biosims (Pty) Ltd	**Date of SAHPRA approval:** 02 August 2022
Product: CLOZAPINE 25 mg OETHMAAN CLOZAPINE 50 mg OETHMAAN CLOZAPINE 100 mg OETHMAAN	**Dosage form and strength:** Each tablet contains: 25 mg/50 mg/100 mg clozapine

PROFESSIONAL INFORMATION – CLEAN COPY

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

CLOZAPINE 25 OETHMAAN, Tablets

CLOZAPINE 50 OETHMAAN, Tablets

CLOZAPINE 100 OETHMAAN, Tablets

WARNING

Because of the significant risk that CLOZAPINE OETHMAAN can cause fatal agranulocytosis, its use should be limited to severely ill schizophrenic patients who are non-responsive to, or intolerant of classic neuroleptic medicinal treatment.

Prescribers should comply fully with the required safety measures. At each consultation a patient receiving CLOZAPINE OETHMAAN should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to "flu-like" complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

Patients who are being treated with CLOZAPINE OETHMAAN must have initially normal leucocyte findings (baseline white blood cell count ≥ 3 500/mm^3 and normal differential blood count) before initiation of treatment. Regular white blood cell (WBC) counts and if possible, absolute neutrophil counts (ANC) should be performed (weekly during the first 18 weeks and at least every two weeks thereafter

throughout treatment and for one month after discontinuation of treatment).

Orthostatic hypotension, with or without syncope, can occur with CLOZAPINE OETHMAAN treatment. Collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation, but they may occur even after the first dose. Therefore patients commencing CLOZAPINE OETHMAAN treatment require close medical supervision.

Seizures can be estimated to occur in association with CLOZAPINE OETHMAAN use at a cumulative incidence at one year of approximately 5 % based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZAPINE OETHMAAN during its clinical testing prior to domestic marketing (i.e. a crude rate of 3,5 %).

Dose appears to be an important predictor of seizure, with a greater likelihood at the higher dosages used. Caution is advised when administering CLOZAPINE OETHMAAN to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZAPINE OETHMAAN, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g. the operation of complex machinery, driving a vehicle, swimming, climbing etc.

Myocarditis

CLOZAPINE OETHMAAN is associated with an increased risk of myocarditis which

has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely (see section 4.4).

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and for palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction (see section 4.4).

If myocarditis or cardiomyopathy are suspected, CLOZAPINE OETHMAAN treatment should be promptly stopped and the patient immediately referred to a cardiologist (see section 4.4).

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine (see section 4.3 and 4.4).

***Hyperglycaemia and Diabetes Mellitus*:**

Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with CLOZAPINE OETHMAAN.

Patients with an established diagnosis of diabetes mellitus who are started on CLOZAPINE OETHMAAN should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes), who are starting treatment with CLOZAPINE OETHMAAN, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with CLOZAPINE OETHMAAN should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when

CLOZAPINE OETHMAAN was discontinued. However, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each **CLOZAPINE 25 OETHMAAN** tablet contains: 25 mg clozapine

Each **CLOZAPINE 50 OETHMAAN** tablet contains: 50 mg clozapine

Each **CLOZAPINE 100 OETHMAAN** tablet contains: 100 mg clozapine

Contains sugar (lactose monohydrate)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

CLOZAPINE 25 OETHMAAN:

Round, light yellow tablets with break notch and embossment.

Diameter: 5,8 to 6,2 mm. Height: 2,7 to 3,1 mm.

CLOZAPINE 50 OETHMAAN:

Round, light yellow tablets with break notch and embossment.

Diameter: 7,8 to 8,2 mm. Height: 3,5 to 4,0 mm.

CLOZAPINE 100 OETHMAAN:

Round, light yellow tablets with break notch and embossment.

Diameter: 8,8 to 10,2 mm. Height: 4,3 to 4,7 mm.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

Treatment-resistant schizophrenia:

CLOZAPINE OETHMAAN is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations and at adequate dosages.

Intolerance is defined as the impossibility of achieving adequate clinical benefit with standard antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Risk of recurrent suicidal behaviour:

CLOZAPINE OETHMAAN is also indicated for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia who are judged to be at chronic risk for re-experiencing suicidal behaviour, based on history and recent clinical state. Suicidal behaviour refers to actions by a patient that put him/herself at high risk for death.

Drug-induced Psychosis during the course of Parkinson's disease:

CLOZAPINE OETHMAAN is indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

The failure of standard treatment is defined as the lack of control of the psychotic symptoms and/or the onset of functionally unacceptable motoric deterioration occurring after the following measures have been taken:

- Withdrawal of anti-cholinergic medication including tricyclic anti-depressants.
- Attempt to reduce the dose of antiparkinsonian medication with dopaminergic effect.

4.2 Posology and method of administration

<u>Posology</u>

The dosage must be adjusted individually and is different for the individual indications. For each patient the lowest effective dose should be used.

Initiation of CLOZAPINE OETHMAAN treatment must be restricted to those patients with a WBC count ≥ 3500/mm^3 (3,5 x 10^9/L) and an absolute neutrophil count (ANC) ≥ 2000/mm^3 (2,0 x 10^9/L), and within standardised normal limits.

Dose adjustment is indicated in patients receiving medicines interacting with clozapine, such as benzodiazepines and medicine with selective serotonin re-uptake (see Section 4.5).

The following dosages for oral administration are recommended:

Treatment-resistant schizophrenia:

Starting therapy: 12,5 mg (half a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg, in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Use in the elderly:

It is recommended to initiate treatment at a particularly low dose (12,5 mg given once on the first day) and to restrict subsequent dose increments to 25 mg per day.

Therapeutic dose range:

In most patients, antipsychotic efficacy can be expected with 300 mg to 450 mg per day given in divided doses. Some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion at bedtime. For maintenance dose see below.

Maximum dose:

A few patients, however, may require larger doses to obtain maximum therapeutic benefit, in which case judicious increments (not to exceed 100 mg per increment) are permissible to a

maximum dose of 900 mg per day. The possibility of increased adverse reactions (in particular seizures) occurring at doses of over 450 mg per day must be considered.

Maintenance dose:

After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. With daily doses not exceeding 200 mg, a single administration in the evening may be appropriate.

Ending therapy:

In the event of planned termination of CLOZAPINE OETHMAAN therapy, a gradual reduction in dose is recommended over a 1 to 2 week period. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Re-starting therapy:

In patients in whom the interval since the last dose of CLOZAPINE OETHMAAN exceeds 2 days, treatment should be re-initiated with 12,5 mg (one-half of a 25 mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see Section 4.4*),* but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Switching from a previous antipsychotic therapy to CLOZAPINE OETHMAAN:

CLOZAPINE OETHMAAN should not be used in combination with other antipsychotic.

When CLOZAPINE OETHMAAN therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to totally discontinue the other antipsychotic therapy before initiating treatment with CLOZAPINE OETHMAAN.

Reducing the risk of suicidal behaviour in schizophrenia and schizoaffective disorder:

The dosage and administration recommendations described in the preceding section Method of administration regarding the use of CLOZAPINE OETHMAAN in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behaviour.

A course of treatment with CLOZAPINE OETHMAAN of at least two years is recommended in order to maintain the reduction of risk for suicidal behaviour. It is recommended that the patient's risk of suicidal behaviour be reassessed after two years of treatment and that thereafter the decision to continue treatment with CLOZAPINE OETHMAAN be re-visited at regular intervals, based on thorough assessments of patient's risk for suicidal behaviour during treatment.

Drug-induced Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed:

The starting dose must not exceed 12,5 mg/day (half a 25 mg tablet), taken in the evening. Subsequent dose increases must be by 12,5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening. Higher doses are associated with significant adverse effects.

The mean effective dose is usually between 25 and 37,5 mg/day.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When ending therapy, a gradual reduction in dose by steps of 12,5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated in (see Section 4.4*).* In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

4.3 Contraindications

- Hypersensitivity to clozapine or any of the ingredients of CLOZAPINE OETHMAAN listed in section 6.1.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- CLOZAPINE OETHMAAN should not be used with other medicines which have a well-known potential to suppress bone marrow function.
- Impaired bone marrow function.
- Convulsions or uncontrolled epilepsy.
- Concomitant use of CLOZAPINE OETHMAAN and carbamazepine.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Glaucoma.
- Circulatory collapse and/or depression of the central nervous system, irrespective of the causes.
- Severe renal or cardiac disorders (e.g, myocarditis).

- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.
- Children under the age of 16 years as safety and efficacy have not been demonstrated.
- Patients at increased risk for venous thromboembolism.

4.4 Special warnings and precautions for use

Orthostatic hypotension, with or without syncope, can occur with CLOZAPINE OETHMAAN treatment. Collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; but they may occur even after the first dose. Therefore, patients commencing CLOZAPINE OETHMAAN treatment require close medical supervision.

Seizure has been estimated to occur in association with CLOZAPINE OETHMAAN use at a cumulative incidence at one year of approximately 5 %, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZAPINE OETHMAAN during its clinical testing prior to domestic marketing (i.e. a crude rate of 3.5 %). Dose appears to be an important predictor of seizure, with a greater likelihood at the higher CLOZAPINE OETHMAAN doses used. Caution should be used in administering CLOZAPINE OETHMAAN to patients having a history of seizures or other predisposing factors.

Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g. the operation of complex machinery, driving a vehicle, swimming, climbing, etc.

Since CLOZAPINE OETHMAAN may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of the patient should be avoided.

Special Precautionary Measures:

Because of the association of CLOZAPINE OETHMAAN with agranulocytosis, the following precautionary measures are mandatory:

CLOZAPINE OETHMAAN should not be used concurrently with medicines associated with a substantial potential to depress bone marrow function. In addition, the concomitant use of long-acting depot anti psychotics should be avoided because of the inability of removing these medicines, which may have the potential to be myelosuppressive, to be rapidly removed from the body in situations where this may be required, e.g. granulocytopenia.

Patients with a ***history of primary bone marrow disorders*** may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting CLOZAPINE OETHMAAN.

Patients who have low WBC counts because of ***benign ethnic neutropenia*** should be given special consideration and may be started on CLOZAPINE OETHMAAN after agreement of a haematologist.

WBC counts and ANC monitoring:

Before starting CLOZAPINE OETHMAAN treatment, a White Blood Cell count and a differential blood count must be performed within 10 days prior to starting CLOZAPINE OETHMAAN treatment to ensure that only patients with normal leukocyte count and normal absolute neutrophil count (ANC) (WBC count ≥ 3 500/mm^3 and ANC ≥ 2000/mm^3) will receive the medicine. After the start of CLOZAPINE OETHMAAN treatment the WBC count and, if possible, ANC must be monitored weekly for 18 weeks and thereafter at least every 2 weeks for one year and thereafter every four weeks throughout treatment, and for 4 weeks after complete discontinuation of CLOZAPINE OETHMAAN.

At each consultation, the patient should be reminded to contact the treating medical practitioner immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. An immediate differential blood count must be performed if any symptoms or signs of an infection occur.

In* case *of low WBC count/ANC*:***

During CLOZAPINE OETHMAAN therapy, if the WBC count falls to between 3500/mm^3 and 3000/mm^3 and/or the ANC falls to between 2000/mm^3 and 1500/mm^3, at least twice weekly haematological evaluations are necessary.

In addition, if, during CLOZAPINE OETHMAAN therapy, the WBC count has dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be done. A substantial drop is defined as a single drop of 3000/mm^3 or more in the WBC count or a cumulative drop of 3000/mm^3 or more within 3 weeks.

Immediate *discontinuation* of CLOZAPINE OETHMAAN treatment is mandatory if the WBC count is less than 3000/mm^3 or the ANC is less than 1500/mm^3 during CLOZAPINE OETHMAAN therapy, WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms

suggestive of infection. Following discontinuation of CLOZAPINE OETHMAAN, haematological evaluation is required until haematological recovery has occurred.

If CLOZAPINE OETHMAAN has been withdrawn and a further fall of WBC count below 2000/mm^3 occurs and/or neutrophil granulocytes decrease below 1000/mm^3, the management of this condition must be guided by an experienced haematologist.

Patients in whom CLOZAPINE OETHMAAN has been discontinued as a result of white blood cell deficiencies (see above), must never be re-exposed to CLOZAPINE OETHMAAN.

Confirmation of the haematological values is recommended by performing two blood counts done on two consecutive days; however, CLOZAPINE OETHMAAN should be discontinued after the first blood count.

Table 1: Blood monitoring during CLOZAPINE OETHMAAN therapy:

Blood cell count		**Action required**
WBC/mm^3	**ANC/mm^3**	
≥ 3500 (> 3,5 x 10^9)	≥ 2000 (> 2,0 x 10^9)	Continue CLOZAPINE OETHMAAN treatment
3000 to 3500 (3,0 x 10^9 to 3,5 x 10^9)	1500 to 2000 (1,5 x 10^9 to 2,0 x 10^9)	Continue CLOZAPINE OETHMAAN treatment, sample blood twice weekly until count stabilise or increase
< 3000 (< 3,0 x 10^9)	< 1500 (< 1,5 x 10^9)	Immediately stop CLOZAPINE OETHMAAN treatment,

		sample daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons:

Patients who have been on CLOZAPINE OETHMAAN for more than 18 weeks and have had the treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and, if possible, ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 2 weeks may be resumed. If CLOZAPINE OETHMAAN treatment has been interrupted for 4 weeks or longer, weekly monitoring is required as for patients never exposed to CLOZAPINE OETHMAAN.

Other precautions:

Eosinophilia

In the event of eosinophilia, it is recommended to discontinue CLOZAPINE OETHMAAN if the eosinophil count rises above 3000/mm^3, and to re-start therapy only after the eosinophil count has fallen below 1000/mm^3.

Thrombocytopenia

In the event of thrombocytopenia, it is recommended to discontinue CLOZAPINE OETHMAAN therapy if the platelet count falls below 50000/mm^3.

Cardiovascular disorders

Orthostatic hypotension, can occur with CLOZAPINE OETHMAAN treatment **(See above*).*** Rarely (about one case per 3000 CLOZAPINE OETHMAAN treated patients), resulting in collapse and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing CLOZAPINE OETHMAAN treatment require close medical supervision. Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may occur. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, CLOZAPINE OETHMAAN should be discontinued.

Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, CLOZAPINE OETHMAAN should be stopped.

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease as severe hypotension and orthostatic hypotension may occur.

<u>Seizures</u>

In patients with a history of seizures, or suffering from cardiovascular or renal disorders (note: severe, renal or cardiovascular disorders are contraindications) the initial dose should be 12,5 mg given once on the first day, and dosage increase should be slow and in small increments.

<u>Anticholinergic effects</u>

CLOZAPINE OETHMAAN exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, CLOZAPINE OETHMAAN has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction ischaemia **(see Section 4.8*).*** On rare occasions these cases have been fatal.

Particular care is necessary in patients who are receiving concomitant medicines known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and anti-parkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

Fever

During CLOZAPINE OETHMAAN therapy, patients may experience transient temperature elevations above 38 °C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered.

Hepatic impairment

Patients with stable pre-existing liver disorders may receive CLOZAPINE OETHMAAN, but need regular liver function tests. In patients in whom, during CLOZAPINE OETHMAAN treatment, symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia

develop, liver function tests should be performed immediately. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with CLOZAPINE OETHMAAN must be discontinued.

CLOZAPINE OETHMAAN treatment may be resumed (see re-starting therapy) only when the liver function tests have returned to normal values. In such cases, liver function should be closely monitored after the reintroduction of the medicine.

Metabolic changes

CLOZAPINE OETHMAAN has been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain.

Hyperglycaemia

On rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma has been reported during CLOZAPINE OETHMAAN treatment in patients with no prior history of hyperglycaemia. While a causal relationship to CLOZAPINE OETHMAAN use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of CLOZAPINE OETHMAAN, and re-challenge produced a recurrence of hyperglycaemia in individual cases. The effect of CLOZAPINE OETHMAAN on glucose metabolism in patients with diabetes mellitus has not been studied. Impaired glucose tolerance, severe hyperglycaemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycaemia. Exacerbation of diabetes should be considered in patients receiving CLOZAPINE OETHMAAN who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia or weakness. In patients with

significant treatment-emergent hyperglycaemia, discontinuation of CLOZAPINE OETHMAAN should be considered.

There is a risk of altering the metabolic balance resulting in impairment of glucose homeostasis and an unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with CLOZAPINE OETHMAAN. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using CLOZAPINE OETHMAAN is recommended.

Weight gain

Weight gain has been observed with CLOZAPINE OETHMAAN use. Clinical monitoring of weight is recommended.

Risk of thromboembolism

Since CLOZAPINE OETHMAAN may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of the patient should be avoided.

Use in elderly:

It is recommended to initiate treatment at a particularly low dose (12,5 mg given once on the first day) and to restrict subsequent dose increments to 25 mg/day.

Clinical studies with CLOZAPINE OETHMAAN did not include sufficient numbers of subjects aged 65 years and over to determine whether or not they respond differently from younger subjects.

Hypotension:

Orthostatic hypotension can occur with CLOZAPINE OETHMAAN treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking CLOZAPINE OETHMAAN. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Elderly patients may also be particularly susceptible to the anticholinergic effects of CLOZAPINE OETHMAAN, such as urinary retention and constipation.

Falls

CLOZAPINE OETHMAAN may cause seizures, somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medicines that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Rebound withdrawal effects

Acute withdrawal reactions have been reported following abrupt cessation of CLOZAPINE OEHMAAN therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary (e.g. because of leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Lactose

CLOZAPINE OETHMAAN contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose

intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take CLOZAPINE OETHMAAN.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic-related interactions:

Medicines known to have a substantial potential to depress bone marrow function should not be used concurrently with CLOZAPINE OETHMAAN (see also Section 4.3 and 4.4*).*

CLOZAPINE OETHMAAN may increase the central nervous system (CNS)-depressive effects of alcohol, mono amine oxidase (MAO)- inhibitors, and other CNS-depressants such as narcotics, antihistamines and benzodiazepines.

Concurrent use with carbamazepine may increase the risk of severe haematological effects.

Concurrent or recent treatment with benzodiazepines or other psychotropic medicines increases the risk of circulatory collapse with cardiac and/or respiratory depression or arrest.

Special care should be taken with the concurrent use of hypotensive, anticholinergic or respiratory depression-producing medicines due to the possibility of additive effects of these medicines.

The concurrent use of CLOZAPINE OETHMAAN and lithium or other CNS-active agents increases the risk of neuroleptic malignant syndrome.

Owing to its anti-α-adrenergic properties, CLOZAPINE OETHMAAN may reduce the blood pressure-increasing effect of norepinephrine or other predominantly a-adrenergic agents and reverse the pressor effect of adrenaline.

Serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where CLOZAPINE OETHMAAN was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Pharmacokinetic-related interactions:

CLOZAPINE OETHMAAN is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. Caution is called for in patients receiving concomitant treatment with other medicines, which are either inhibitors or inducers of these enzymes.

With tricyclic antidepressants, phenothiazines and type I_c anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far. On theoretical grounds, however, it is possible that the plasma levels of such medicines are increased by CLOZAPINE OETHMAAN, so it may be appropriate to use them at doses lower than usually prescribed.

Concomitant administration of medicines known to induce cytochrome P450 enzymes may reduce the plasma levels of CLOZAPINE OETHMAAN and may be associated with the recurrence of psychotic symptoms:

- Substances known to induce the activity of 3A4 and with reported interactions with CLOZAPINE OETHMAAN include, carbamazepine, phenytoin and rifampicin.

- Known inducers of 1A2 include, omeprazole and nicotine. In cases of sudden cessation of nicotine abuse, the plasma CLOZAPINE OETHMAAN concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of medicines known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of CLOZAPINE OETHMAAN, possibly resulting in adverse effects.

- Medicines known to inhibit the activity of the major isozymes involved in the metabolism of CLOZAPINE OETHMAAN and with reported interactions include cimetidine, erythromycin (3A4), fluvoxamine (1A2), sertraline, fluoxetine, citalopram and paroxetine.
- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, may increase clozapine plasma concentrations; no interactions have been reported to date, however.
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50 % following a 5-day caffeine-free period.
- Elevated clozapine plasma concentrations also have been reported in patients receiving the medicine in combination with selective serotonin re-uptake inhibitors such as paroxetine (1A2), sertraline, fluoxetine, citalopram or fluvoxamine.

Competition of binding sites on plasma proteins can lead to changes in plasma levels of CLOZAPINE OETHMAAN or other medicines which bind strongly to protein e.g. warfarin.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy:

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine. However, the safe use of CLOZAPINE OETHMAAN in pregnant women has not been established.

Neonates exposed to clozapine during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation:

Animal studies suggest that clozapine is excreted in breast milk; therefore, mothers receiving CLOZAPINE OETHMAAN should not breast-feed.

Women of childbearing potential:

Some female patients treated with antipsychotics other than CLOZAPINE OETHMAAN may become amenorrhoeic. A return to normal menstruation may occur as a result of switching from other antipsychotics to CLOZAPINE OETHMAAN. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

4.7 Effects on ability to drive and use machines

Owing to the ability of CLOZAPINE OETHMAAN to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

4.8 Undesirable effects

Infections and infestations:

Frequency not known: Sepsis*.

Blood and lymphatic system disorders:

Frequent: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis.

Less frequent: Granulocytopenia and agranulocytosis may occur particularly during the first 18 weeks of therapy. Although generally reversible after termination of therapy, agranulocytosis may prove to be fatal. Anaemia, thrombocytopenia, thrombocythaemia.

Immune system disorders:

Frequency not known: Angioedema*, leukocytoclastic vasculitis*, drug rash with eosinophilia and systemic symptoms (DRESS)*.

Endocrine disorders:

Frequency not known: Pseudophaeochromocytoma*.

Metabolism and nutrition disorders:

Frequent: Weight gain.

Less frequent: Impaired glucose tolerance, diabetes aggravated, ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia.

Frequency not known: Obesity*.

Psychiatric disorders

Frequent: Dysarthria

Less frequent: Restlessness, agitation, dysphemia.

Nervous system disorders:

Frequent: Drowsiness, sedation, dizziness, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks.

Less frequent: Neuroleptic malignant syndrome (with or without concomitant use of lithium), confusion, delirium, tardive dyskinesia, obsessive compulsive symptoms. CLOZAPINE OETHMAAN lowers the seizure threshold and may cause electro-encephalogram (EEG) disturbances, including occurrence of spike and wave complexes. If seizures occur, the dosage should be lowered, and, if necessary, anticonvulsant therapy initiated.

With anticonvulsant agents, the possibility of a pharmacokinetic interaction should be considered.

Frequency not known: Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless leg syndrome*

Eye disorders:

Frequent: Blurred vision.

Cardiac disorders*:*

Frequent: Tachycardia, ECG changes

Less frequent: Circulatory collapse, dysrhythmias, myocarditis, pericarditis/pericardial effusion, cardiomyopathy, cardiac arrest.

Frequency not known: Myocardial infarction *,**, myocarditis*,**, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*.

Vascular disorders*:*

Frequent: Hypertension, postural hypotension, syncope.

Less frequent: Thromboembolism.

Frequency not known: Hypotension*, venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis.

Respiratory, thoracic and mediastinal disorders*:*

Less frequent: Aspiration of ingested food, as a consequence of dysphagia, pneumonia and lower respiratory tract infection which may be fatal, sleep apnoea syndrome, respiratory depression/arrest.

Frequency not known: Pleural effusion*, nasal congestion*.

Gastrointestinal disorders*:*

Frequent: Constipation, hypersalivation, nausea, vomiting, anorexia, dry mouth.

Less frequent: Dysphagia, parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction.

Frequency not known: Megacolon*,**, intestinal infarction/ischaemia *,**,intestinal necrosis*,**, intestinal ulceration*,**, and intestinal perforation*,**, diarrhoea*, abdominal discomfort/heartburn/dyspepsia*, colitis*

Hepato-biliary disorders*:*

Frequent: Asymptomatic elevations in liver enzymes.

Less frequent: Hepatitis, cholestatic jaundice and acute pancreatitis, fulminant hepatic necrosis.

Frequency not known: Hepatic steatosis*, hepatic necrosis*, hepatotoxicity*, hepatic fibrosis*, hepatic cirrhosis*, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant*.

Skin and subcutaneous tissue disorders*:*

Less frequent: Skin reactions.

Frequency not known: Pigmentation disorder*.

Musculoskeletal and connective tissue disorders:

Frequency not known: Rhabdomyolysis*, muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematosus*.

Renal and urinary disorders*:*

Frequent: Urinary incontinence, urinary retention.

Less frequent: Interstitial nephritis.

Frequency not known: Renal failure*, Nocturnal enuresis*.

Pregnancy, puerperium and perinatal conditions:

Frequency not known: Drug withdrawal syndrome neonatal (see 4.6)

Reproductive system and breast disorders*:*

Less frequent: Priapism.

Frequency not known: Retrograde ejaculation*.

General disorders and administration site conditions*:*

Frequent: Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation.

Less frequent: Sudden and unexplained death has been reported.

Frequency not known: Polyserositis*.

Investigations:

Less frequent: Increased creatine phosphokinase (CPK).

Injury, poisoning and procedural complications:

Frequency not known: Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)*

*Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.

**These adverse drug reactions were sometimes fatal.

Reporting of suspected adverse reactions

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

4.9 Overdose:

Fatal overdosage has been reported at dosages above 2 000 mg.

Symptoms:

Dry mouth, dry skin, sleepiness, lethargy, coma, areflexia, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions, hypersalivation, mydriasis, blurred vision, thermolability, tachycardia, hypotension, collapse, cardiac arrythmias, aspiration, pneumonia, dyspnoea, heart block, respiratory depression or failure.

Treatment:

Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-based balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of "reverse epinephrine effect".

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2. 6. 5 Tranquilizers (miscellaneous structures)

ATC Code: N05AH02

Clozapine is an atypical antipsychotic agent. It has weak dopamine receptor blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor. In addition, it possesses noradrenolytic, anticholinergic, antihistaminergic and arousal reaction inhibiting properties.

5.2 Pharmacokinetic properties

The absorption of orally administered clozapine is 90 to 95 % and is independent of food intake. Clozapine is subject to moderate first-pass metabolism and has an absolute bioavailability of approximately 50 to 60 %. Peak plasma levels are reached after approximately 1 to 3 hours, with a range of 0,5 to 6 hours, and the distribution volume at steady state is 1,6 ± 1,1 l/kg.

The plasma protein binding is approximately 95 %.

The elimination is biphasic with a mean terminal half-life of 12 hours.

Clozapine is almost completely metabolized before excretion. Only one of the metabolites (desmethyl-metabolite) was found to be active. The activity resembles that of clozapine, although it is of shorter duration. About 50 % of the administered dose is excreted as metabolites via the urine and 30 % via the faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica,

lactose monohydrate,

magnesium stearate,

maize starch,

microcrystalline cellulose,

polyvinylpyrrolidone K25,

sodium lauryl sulphate,

sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in a dry place, below 25 °C.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

CLOZAPINE 25 OETHMAAN, CLOZAPINE 50 OETHMAAN and CLOZAPINE 100 OETHMAAN:

White opaque PVC / Aluminium blister strips containing 10 tablets each.

10 (10) blister strips to be packed into a carton i.e. 100 tablets per carton.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenberg Roads

Victory Park

Johannesburg

2195

8 REGISTRATION NUMBER(S)

CLOZAPINE 25 OETHMAAN: 37/2.6.5/0188

CLOZAPINE 50 OETHMAAN: 37/2.6.5/0189

CLOZAPINE 100 OETHMAAN: 37/2.6.5/0190

9 DATE OF FIRST AUTHORISATION

Date of registration: 25 November 2005

10 DATE OF REVISION OF THE TEXT

02 August 2022