1.3.2 PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S5

ASPEN CLOZAPINE 25 mg tablet

Clozapine

Contains sugar: Lactose monohydrate 45,25 mg

ASPEN CLOZAPINE 100 mg tablet

Clozapine

Contains sugar: Lactose monohydrate 181,00 mg

1. FATAL AGRANULOCYTOSIS

ASPEN CLOZAPINE can cause a dangerous lowering of your white blood cell count, called agranulocytosis, which may cause death. Your doctor will request you to go to a laboratory to have a blood count done before you start treatment, weekly (for the first 18 weeks of treatment), two-weekly whilst on treatment and four weeks after stopping treatment with ASPEN CLOZAPINE. If you develop flu-like symptoms such as a fever, a sore throat or any other evidence of an infection, it is extremely important for you or your caregiver to report this to your doctor immediately. You will have to go to a laboratory to do a blood cell count. Your doctor will keep a record of the blood cell count results.

2. ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is a form of low blood pressure that happens when you stand up from sitting or lying down. ASPEN CLOZAPINE can cause orthostatic

hypotension with or without loss of consciousness. This collapse can include heart arrest (your heart suddenly stops pumping or respiratory arrest (when you stop breathing). This is more likely to occur when you start treatment or during the phase where your doctor is still adjusting your dose to determine the right dose for you, but this has occurred in patients after taking the first dose of ASPEN CLOZAPINE. It is very important that you are closely monitored by medical staff when you start treatment with ASPEN CLOZAPINE.

3. FITS (SEIZURES)

Fits have been reported with the use of ASPEN CLOZAPINE. Take special care if you have a history of fits or any factors that make you more likely to experience fits. You should not engage in activities where a sudden loss of consciousness could cause serious risk to you e.g. operation of machinery, driving, swimming or climbing.

4. HYPERGLYCAEMIA AND DIABETES MELLITUS (sugar diabetes)

Hyperglycaemia, or high blood sugar which may be associated with a high level of ketones (byproducts when the body breaks down fat for energy), coma or death have been reported in patients taking ASPEN CLOZAPINE. If you have sugar diabetes your blood sugar control may change when you are on treatment with ASPEN CLOZAPINE.

If you have risk factors for developing diabetes such as being overweight or a family history of diabetes your blood sugar should be closely monitored when you start ASPEN CLOZAPINE. Symptoms of high blood sugar often include being very thirsty, forming or passing an abnormally large quantity of urine, more often, excessive eating or increased appetite and weakness. If you experience any of these symptoms you should go for a blood sugar test. You may have to continue

with treatment for high blood glucose levels even after your treatment with ASPEN CLOZAPINE has been stopped.

5. MYOCARDITIS

Inflammation of the heart muscle (myocarditis) has been reported and can cause death. There is an increased risk for myocarditis during the first two months of starting treatment with ASPEN CLOZAPINE.

If you experience any of the following symptoms, especially during the first two months of starting ASPEN CLOZAPINE treatment you should immediately see a cardiologist (heart specialist):

- **It persistently feels as if your heart beats faster during rest.**
- **It feels as if your heart is beating too hard or too fast, skipping a beat, or fluttering.**
- **It feels as if your heart is beating irregularly.**
- **If you have chest pain, unexplained fatigue.**
- **If it is difficult for you to breathe or if it feels as if you are breathing too fast.**

You cannot be restarted on treatment with ASPEN CLOZAPINE if you previously developed myocarditis (inflammation of your heart muscle).

6. HYPOMOTILITY (slow moving of your gut)

ASPEN CLOZAPINE may cause abnormally slow contractions of the muscles in your digestive tract. This may lead to constipation, blockage in the digestive tract, stool becoming stuck in the large bowel, torn bowel or a loss of blood supply to the digestive tract. It is important to drink enough fluids, stay active and include enough fibre in your diet. Your doctor will check any other medicines that you take with ASPEN CLOZAPINE as these may increase the probability of slow

contractions of the muscles in your digestive tract. If you develop constipation you should contact your doctor immediately.

Read all of this leaflet carefully before you start taking ASPEN CLOZAPINE

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- ASPEN CLOZAPINE has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What ASPEN CLOZAPINE is and what it is used for
2. What you need to know before you take ASPEN CLOZAPINE
3. How to take/use ASPEN CLOZAPINE
4. Possible side effects
5. How to store ASPEN CLOZAPINE
6. Contents of the pack and other information

1. What ASPEN CLOZAPINE is and what it is used for

ASPEN CLOZAPINE belongs to a group of medicines called antipsychotics.

ASPEN CLOZAPINE is used to treat people with schizophrenia where all other options have failed or cannot be tolerated.

ASPEN CLOZAPINE is used to reduce the risk of ongoing suicidal behaviour if you schizophrenia and is based on your history and recent clinical state.

ASPEN CLOZAPINE is used to treat severe disturbances in the thoughts, emotions and

behaviour related to Parkinson's disease where other medicines have not worked or can't be tolerated.

2. What you need to know before you take ASPEN CLOZAPINE

Do not take ASPEN CLOZAPINE if you:

- Are hypersensitive (allergic) to clozapine or any of the other ingredients of ASPEN CLOZAPINE.
- Are not able to have regular blood tests.
- Have ever been told you have a low white blood cell count (e.g. leucopoenia or agranulocytosis), especially if this was caused by medicines: this does not apply if you have had low white blood cell count caused by previous chemotherapy.
- Had to stop using ASPEN CLOZAPINE previously because of severe side effects such as agranulocytosis (severe and dangerous lowered white blood cell counts or heart problems.
- Suffer from bone marrow disease or have ever suffered from bone marrow disease.
- Suffer from uncontrolled epilepsy (seizures or fits).
- Have an acute mental illness caused by alcohol or drugs (e.g. narcotics).
- Suffer from reduced consciousness and severe drowsiness.
- Suffer from circulatory collapse (significant drop in blood pressure) which may occur as a result of severe shock.
- Suffer from any severe kidney disease.
- Suffer from myocarditis (an inflammation of the heart muscle).
- Suffer from any other severe heart disease.
- Have symptoms of active liver disease such as jaundice (yellow colouring of the skin and eyes, feeling sick and loss of appetite).
- Suffer from any other severe liver disease.

- Suffer from paralytic ileus (your bowel does not work properly and you have severe constipation).
- Use any medicine that stops your bone marrow from working properly.
- Use any medicine that reduces the number of white cells in your blood.
- ASPEN CLOZAPINE must not be given to anyone who is unconscious or in a coma.
- Smoke tobacco, as smoking may reduce the effectiveness of your ASPEN CLOZAPINE and to stop smoking may increase the effectiveness of your ASPEN CLOZAPINE dose.
- Have glaucoma (increased pressure in the eye).
- Are pregnant or breastfeeding your baby.

ASPEN CLOZAPINE should not be used in children under the age of 16 years of age (see Do not take ASPEN CLOZAPINE).

Warnings and precautions

Take special care with ASPEN CLOZAPINE if you have or ever had:

- Blood clots or family history of blood clots, as ASPEN CLOZAPINE has been associated with the forming of blood clots.
- Diabetes: Considerably high blood sugar levels, have occurred in patients with or without diabetes mellitus.
- Prostate problems or difficulty in urinating.
- Any kidney or liver disease.
- Severe constipation or if you are taking medicines which cause constipation (such as anticholinergics – medicines that inhibit nerve impulses). Your doctor will have to treat this in order to avoid further complications.
- Epilepsy.
- Large intestine diseases.
- Abdominal surgery.

- A heart disease or family history of abnormal conduction in the heart (long QT syndrome).
- A risk of having a stroke, for example if you have high blood pressure, heart problems or blood vessel problems in the brain.
- Signs of a cold, fever, flu-like symptoms, sore throat or any other infection: You will have to have an urgent blood test to check if your symptoms are related to your medicine.
- A sudden rapid increase in body temperature, rigid muscles which may lead to unconsciousness (neuroleptic malignant syndrome) as you may be experiencing a serious side effect which requires immediate treatment.
- Fast and irregular heartbeat, even when you are at rest, palpitations, breathing problems, chest pain or unexplained tiredness: Your doctor will need to check your heart and if necessary, refer you to a cardiologist immediately.
- Experience nausea (feeling sick), vomiting (being sick) and/or loss of appetite: Your doctor will need to check your liver.

Before you start taking ASPEN CLOZAPINE, your doctor will ask about your medical history and do a blood test to ensure that your white blood cell count is normal: It is important to make sure, as your body needs white blood cells to fight infections.

Make sure that you have regular blood tests before you start treatment, during treatment and after you stop treatment with ASPEN CLOZAPINE.

- Your doctor will tell you exactly when and where to have the tests. ASPEN CLOZAPINE should only be taken if you have a normal blood count.
- ASPEN CLOZAPINE can cause a serious decrease in the number of white cells in your blood (agranulocytosis). Only regular blood tests can tell the doctor if you are at risk of developing agranulocytosis.
- During the first 18 weeks of treatment, tests are needed once a week. Afterwards, tests

are needed at least every two weeks and four weeks after stopping treatment with ASPEN CLOZAPINE.

- If there is a decrease in the number of white blood cells, you will have to stop ASPEN CLOZAPINE treatment immediately. Your white blood cells should then return to normal.
- You will need to have blood tests for another 4 weeks after the end of ASPEN CLOZAPINE treatment.

Your doctor will also do a physical examination before starting treatment. Your doctor may do an electrocardiogram (ECG) to check your heart, but only if this is necessary for you, or if you have any special concerns.

If you have a liver disorder you will have regular liver function tests as long as you continue to take ASPEN CLOZAPINE.

If you suffer from high levels of sugar in the blood (diabetes) your doctor may regularly check your level of sugar in the blood.

ASPEN CLOZAPINE may cause changes in blood lipids. ASPEN CLOZAPINE may cause weight gain. Your doctor may monitor your weight and blood lipid level.

If ASPEN CLOZAPINE makes you feel light-headed, dizzy or faint, be careful when getting up from a sitting or lying position.

If you have to undergo surgery or if for some reason you are unable to walk around for a long time, discuss with your doctor the fact that you are taking ASPEN CLOZAPINE. You may be at risk of thrombosis (blood clotting within a vein).

Children and adolescents under 16 years

If you are under 16 years of age you should not use ASPEN CLOZAPINE as there is not enough information on its use in that age group.

Older people (aged 60 years and over)

Older people (aged 60 years and over) may be more likely to have the following side effects

during treatment with ASPEN CLOZAPINE: faintness or light-headedness after changing position, dizziness, fast heartbeat, difficulty in passing urine, and constipation.

Tell your doctor or pharmacist if you suffer from a condition called dementia.

Other medicines and ASPEN CLOZAPINE

Always tell your healthcare professional if you are taking any other medicines (this includes complementary or traditional medicines).

Tell your doctor if you are taking any of the following medicines:

- Medicines used to treat depression such as lithium, fluvoxamine, tricyclic antidepressants, MAO inhibitors including linezolid, citalopram, paroxetine, fluoxetine or sertraline.
- Medicines used to treat pain such as codeine, oxycodone, or morphine as this may lead to life-threatening digestive tract complications.
- Other antipsychotic medicines used to treat mental illnesses such as pyrazine.
- Benzodiazepines and other medicines used to treat anxiety or sleep disturbances.
- Narcotics and other medicines which can affect your breathing.
- Medicines used to control epilepsy such as phenytoin and valproic acid.
- Medicines used to treat high or low blood pressure such as adrenaline and noradrenaline.
- Warfarin, a medicine used to prevent blood clots.
- Antihistamines, medicines used for colds or allergies such as hay fever.
- Anticholinergic medicines, which are used to relieve stomach cramps, spasms and travel sickness.
- Medicines used to treat Parkinson’s disease.
- Digoxin, a medicine used to treat heart problems.

- Medicines used to treat a fast or irregular heartbeat.
- Some medicines used to treat stomach ulcers, such as omeprazole or cimetidine.
- Some antibiotic medicines, such as erythromycin and rifampicin.
- Some medicines used to treat fungal infections (such as ketoconazole) or viral infections (such as protease inhibitors, used to treat HIV infections).
- Atropine, a medicine which may be used in some eye drops or cough and cold preparations.
- Adrenaline, a medicine used in emergency situations.
- Hormonal contraceptives (birth-control tablets).

ASPEN CLOZAPINE with food and drink

Do not drink alcohol during treatment with ASPEN CLOZAPINE.

Tell your doctor if you smoke and how often you have drinks containing caffeine (coffee, tea, cola).

Sudden changes in your smoking habits or caffeine drinking habits can also change the effects of ASPEN CLOZAPINE.

Your doctor will advise you on the dietary requirements to ensure normal bowel movements during your treatment with ASPEN CLOZAPINE. Sufficient fluid intake (e.g. water), food high in fibre (e.g. wholegrain breakfast cereal, whole-wheat pasta, wholegrain bread, fruit, vegetables) and regular physical activity is recommended. Your healthcare provider will also advise on the dietary requirements on how to manage an increase in your blood sugar. You should reduce your intake of sugar and sugary drinks (e.g. fruit juice) (see Take Special care with ASPEN CLOZAPINE and POSSIBLE SIDE EFFECTS).

Pregnancy and breastfeeding

You should not be treated with ASPEN CLOZAPINE if you are pregnant or breastfeeding your baby.

The safety of ASPEN CLOZAPINE in pregnancy and breastfeeding has not been established.

If you are being treated with ASPEN CLOZAPINE you should not breastfeed your baby.

If you are pregnant or breastfeeding your baby, please consult your healthcare provider for advice before taking/receiving ASPEN CLOZAPINE.

Driving and using machines

Since adverse reactions such as blurred vision, dizziness, drowsiness and visual disturbances have been reported in patients receiving ASPEN CLOZAPINE, you should not drive, use machinery or perform any tasks that require concentration, until you are certain that ASPEN CLOZAPINE does not adversely affect your ability to do so (see POSSIBLE SIDE EFFECTS).

ASPEN CLOZAPINE contains lactose which may have an effect on the control of your blood sugar if you have diabetes mellitus. If you have the rare hereditary conditions of lactose/fructose or galactose intolerance, you should not take ASPEN CLOZAPINE.

3. HOW TO TAKE ASPEN CLOZAPINE

Do not share medicines prescribed for you with any other person. You take ASPEN CLOZAPINE for your condition only.

Always take ASPEN CLOZAPINE exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

In order to minimise the risk of low blood pressure, seizures and drowsiness it is necessary that your doctor increases your dose gradually.

Your doctor will perform blood tests before treating you with ASPEN CLOZAPINE .

It is important that you do not change your dose or stop taking ASPEN CLOZAPINE without asking your doctor first.

If you are 60 years or older, your doctor may start you on a lower dose and increase it more

gradually because you might be more likely to develop some unwanted side effects.

The usual starting dose is 12,5 mg (one half of a 25 mg tablet) once or twice on the first day followed by 25 mg once or twice on the second day. Swallow the tablet with water. If tolerated well, your doctor will then gradually increase the dose over the next 2 to 3 weeks until a dose up to 300 mg per day is reached. Thereafter, if necessary, your doctor may decide to further increase your dose.

If you have the impression that the effect of ASPEN CLOZAPINE is too strong or too weak for you, tell your doctor or pharmacist.

If you take more ASPEN CLOZAPINE than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

See section POSSIBLE SIDE EFFECTS for symptoms that may indicate overdose.

If you forget to take/missed a dose of ASPEN CLOZAPINE

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, leave out the forgotten tablets and take the next dose at the right time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking ASPEN CLOZAPINE

Do not stop taking ASPEN CLOZAPINE without asking your doctor, because your original symptoms may come back and you might get withdrawal reactions. These reactions include sweating, headache, nausea (feeling sick), vomiting (being sick) and diarrhoea.

If you have any of the above signs, tell your doctor straight away. These signs may be

followed by more serious side effects unless you are treated immediately.

Your doctor will advise you on how to reduce your daily dose. If you have to stop ASPEN CLOZAPINE treatment suddenly, you will have to be checked by your doctor.

4. POSSIBLE SIDE EFFECTS

ASPEN CLOZAPINE can have side effects.

Not all side effects reported for ASPEN CLOZAPINE are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking ASPEN CLOZAPINE, please consult your doctor, pharmacist or other healthcare provider for advice.

If any of the following happens, stop taking ASPEN CLOZAPINE and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Constipation, cramping or failure to pass gas may be signs and symptoms of bowel obstruction or any abdominal discomfort; your doctor will have to treat this in order to avoid further complications.
- Angioedema: Swelling of your eyes, mouth, lips, tongue and throat with difficulty in breathing or red welts that suddenly appear, especially near the eyes and lips, but also on the hands, feet, and the inside of the throat, including burning, painful, swollen, sometimes itchy areas, discoloured patches or rash on the hands, feet, face, or genitals. These may be symptoms of a condition called angioedema.
- Signs of a cold, fever, flu-like symptoms, sore throat or any other infection. You will have to have an urgent blood test to check if your symptoms are related to your ASPEN CLOZAPINE treatment.
- Increased thirst, headaches, trouble concentrating, blurred vision, frequent urination, weakness/tiredness, weight loss as these may be symptoms of hyperglycaemia (high blood sugar).

- Seizures (fits) can cause changes in your behaviour, movements or feelings, and in levels of consciousness.
- Fast heartbeat, stopped heart beat (cardiac arrest), disorders of the heart muscle (cardiomyopathy); inflammation of the heart muscle (myocarditis) or the membrane surrounding the heart muscle (pericarditis), fluid collection around the heart (pericardial effusion), fainting and muscle weakness due to a significant drop in blood pressure (circulatory collapse), and/or an abnormal heart beat (dysrhythmia).
- Sudden fainting or sudden loss of consciousness with muscle weakness (syncope).
- Diabetes mellitus (sugar diabetes).
- Fever, muscle aches, joint pain, blood in the urine or stool, abdominal pain, vomiting, cough, numbness or weakness, as these may be symptoms of a condition called hypersensitivity vasculitis or inflammation of small blood vessels.
- High blood pressure, severe sweating, headache, paleness in the face (pallor), rapid heartbeat, shortness of breath, tremors, as these may be symptoms of a tumour of the adrenal gland.
- High levels of white blood cells (leucocytosis), high levels of a specific type of white blood cell (eosinophilia), lack of white blood cells (agranulocytosis), low levels of red blood cells (anaemia), low levels of platelets in the blood (thrombocytopenia), too many platelets are produced in the bone marrow (thrombocythaemia), or a decrease in the number of white blood cells (leucocytes) found in the blood (leucopoenia)
- Signs of a respiratory tract infection or pneumonia such as fever, coughing, difficulty in breathing, wheezing.
- Severe burning upper abdominal pain, extending to the back accompanied by nausea and vomiting due to inflammation of the pancreas.
- Nausea (feeling sick), vomiting (being sick) and/or loss of appetite. Your doctor will need to check your liver.

- Acute onset of shortness of breath, chest pain, anxiety as these may be associated with the development of a blood clot in your lung/s.
- Fever and chills, very low body temperature, urinating less than normal, rapid pulse and breathing, nausea, vomiting, diarrhoea as these may be symptoms associated with the development of sepsis (this occurs when chemicals released into the bloodstream to fight the infection trigger inflammatory responses throughout the body).
- Blood sugar levels of 600 mg/dL or higher, excessive thirst, dry mouth, increased urination, warm, dry skin, fever, drowsiness, confusion, hallucinations as these may be symptoms of a life-threatening metabolic disorder.
- Thirst, frequent urination, nausea, abdominal pain, weakness, fruity-scented breath and confusion as these may be symptoms of a serious complication of diabetes that occurs when your body produces high levels of blood acids called ketones (ketoacidosis).
- Fever, altered mental status, muscle rigidity, and autonomic dysfunction as these may be symptoms of a condition called neuroleptic malignant syndrome (NMS) that is life-threatening.
- Persistent painful erection of the penis. If you have an erection which lasts more than 4 hours immediate medical treatment may be needed in order to avoid further complications.

Tell your doctor if you notice any of the following:

The following side effects have been frequently reported:

- Constipation;
- weight gain;
- impaired glucose tolerance, high cholesterol;
- unclear speech;
- drowsiness, sedation;

- increased salivation;
- dry mouth;
- sweating and difficulty in temperature regulation;
- blurred vision;
- decreased appetite.

The following side effects have been reported less frequently:

- Agitation, restlessness, slurred speech;
- dizziness, headache;
- rigidity, tremors.

The following side effects have been reported but the frequency is unknown:

- Nasal congestion;
- pigmentation disorder;
- muscle weakness, muscle pain.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8
Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

By reporting side effects, you can help provide more information on the safety of ASPEN CLOZAPINE.

5. How to store ASPEN CLOZAPINE

Store in a dry place at or below 25°C.

Protect from moisture and light.

Keep in original packaging until required for use.

Do not store in a bathroom.

Do not use after the expiry date stated on the label.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

6. Contents of the pack and other information

What ASPEN CLOZAPINE contains

ASPEN CLOZAPINE 25 mg:

The active substance is 25 mg of clozapine.

The other ingredients are lactose monohydrate, magnesium stearate, maize starch, povidone K30, purified talc and silica colloidal anhydrous.

ASPEN CLOZAPINE 100 mg:

The active substance is 100 mg of clozapine.

The other ingredients are lactose monohydrate, magnesium stearate, maize starch, povidone K30, purified talc and silica colloidal anhydrous.

What ASPEN CLOZAPINE looks like and contents of the pack

ASPEN CLOZAPINE 25 mg and ASPEN CLOZAPINE 100 mg are round, flat, bevel edged, pale yellow tablets with a pressure sensitive bisect on one side.

ASPEN CLOZAPINE 25 mg and ASPEN CLOZAPINE 100 mg are available in either blister packs or HDPE bottles

- The tablets are packed in green or translucent polyvinyldene chloride coated polyvinylchloride, aluminium foil blisters, in strips of 10 tablets. The blister strips will be packed into a unit carton which will be made up of cardboard in packs of 100 tablets or
- The tablets are packed in HDPE bottles closed with a polypropylene or HDPE screw on cap with a pressure sensitive wad, available in packs of 100 tablets.

Not all packs and pack sizes are necessarily marketed.

Holder of Certificate of Registration

PHARMACARE LTD

Healthcare Park

Woodmead 2191

Hotline: 0800 122 912 (South Africa)

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