1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ASPEN CLOZAPINE 25 mg (tablet)

ASPEN CLOZAPINE 100 mg (tablet)

WARNINGS

1. FATAL AGRANULOCYTOSIS

Because of the significant risk that ASPEN CLOZAPINE 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 ASPEN CLOZAPINE should be reminded to contact the treating medical practitioner 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 and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients who are being treated with ASPEN CLOZAPINE must initially have normal

leucocyte findings (baseline white blood cell count ≥ 3 500/mm³ and normal differential blood count) before initiation of treatment. Regular white blood cell (WBC) counts and if possible, absolute neutrophil counts (ANC) (weekly during the first 18 weeks and at least every two weeks thereafter throughout treatment and for one month after discontinuation of treatment) should be performed.

2. ORTHOSTATIC HYPOTENSION

Orthostatic hypotension, with or without syncope, can occur with ASPEN CLOZAPINE 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; however, they may occur even after the first dose. Therefore, patients commencing ASPEN CLOZAPINE treatment require close medical supervision.

3. SEIZURES

Seizures can be estimated to occur in association with ASPEN CLOZAPINE use, at a cumulative incidence at one year, of approximately 5 % based on the occurrence of one or more seizures in 61 of 1 743 patients exposed to ASPEN CLOZAPINE during its clinical testing prior to domestic marketing (i.e. a crude rate of 3,5 %). Dose appears to be an important predictor of seizures with a greater likelihood at higher dosages used. Caution is advised when administering ASPEN CLOZAPINE to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizures associated with ASPEN 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.

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 ASPEN CLOZAPINE. Patients with an established diagnosis of diabetes mellitus who are started on ASPEN CLOZAPINE 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 ASPEN CLOZAPINE should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with ASPEN CLOZAPINE should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when ASPEN CLOZAPINE was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of ASPEN CLOZAPINE.

5. MYOCARDITIS

ASPEN CLOZAPINE is associated with an increased risk of myocarditis which may be fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported (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/or palpitations, dysrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms which mimic myocardial infarction (see section 4.4). If myocarditis or cardiomyopathy are suspected, ASPEN CLOZAPINE 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 section 4.4).

6. SEVERE LIFE-THREATENING HYPOMOTILITY

Dose-dependent ASPEN CLOZAPINE-induced gastrointestinal (GI) hypomotility may be severe or life-threatening and sometimes fatal. Severe life-threatening hypomotility may lead to severe ileus constipation, bowel obstruction, faecal impaction, faecaloma, megacolon, bowel perforation and gut ischaemia.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of ASPEN CLOZAPINE 25 mg contains 25 mg of clozapine.

Contains sugar: Lactose monohydrate 45,25 mg

Each tablet of ASPEN CLOZAPINE 100 mg contains 100 mg of clozapine

Contains sugar: Lactose monohydrate 181,00 mg.

3. PHARMACEUTICAL FORM

Tablets

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.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment-resistant schizophrenia

ASPEN CLOZAPINE 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 improvements 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 of tardive dyskinesia).

Risk of recurrent suicidal behaviour

ASPEN CLOZAPINE 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 which put him or herself at high risk for death.

Medicine-induced psychosis during the course of Parkinson's disease

ASPEN CLOZAPINE 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

Posology

Adults

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

Initiation of ASPEN CLOZAPINE treatment must be restricted to those patients with a WBC count ≥ 3 500/mm^3 (3,5x10^9/L) and an absolute neutrophil count (ANC) ≥ 2 000/mm^3 (2,0x10^9/L), and within standardised normal limits.

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

The following dosages for oral administration are recommended:

Treatment-resistant schizophrenia:

Starting therapy: The starting dose is 12,5 mg (half a 25 mg tablet) once or twice daily on the first day, followed by one or two tablets of 25 mg on the second day. If well tolerated, the dosage may be increased in increments of 25 mg to 50 mg per day, to achieve a dose of 300 mg a day after 2 to 3 weeks. If necessary, the dosage can be increased to the recommended maximum dosage of 600 mg a day in increments of 50 to 100 mg per week twice or preferably, once a week.

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 ASPEN CLOZAPINE therapy, a gradual reduction in dose is recommended over a 1 to 2 week period. If abrupt discontinuation is necessary (e.g. because of leucopoenia), 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.

Resumption of therapy:

If therapy is to be restarted (the last dose of ASPEN CLOZAPINE was taken longer than 2 days ago) the first dose should be 12,5 mg once or twice on the first day. If this initial dose is well tolerated, the dosage may be increased/ titrated to the therapeutic dose 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 medicine to ASPEN CLOZAPINE:

The use of ASPEN CLOZAPINE in combination with other antipsychotic medicines is not recommended.

When ASPEN CLOZAPINE therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of the other anti-psychotics be reduced or discontinued by gradual lowering of the dose. Based on the clinical circumstances, the prescribing medical practitioner should judge whether or not to totally discontinue the other antipsychotic therapy before initiating treatment with ASPEN CLOZAPINE.

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

The dose and administration recommended were described in the preceding section.

Method of administration of ASPEN CLOZAPINE 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 ASPEN CLOZAPINE 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 ASPEN CLOZAPINE be re-visited at regular intervals, based on thorough assessments of the 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 which 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 (see section 4.4). In this situation, careful psychotic monitoring of patients is essential, since symptoms may recur quickly.

Special populations

Elderly

The recommended initial dosage at a particularly low dose is 12,5 mg (half a 25 mg tablet) on the first day. The dosage may be increased in increments of not more than 25 mg per day.

Paediatric population

No data are available (see section 4.3).

Method of administration

For oral administration.

4.3. Contraindications

ASPEN CLOZAPINE is contraindicated in:

- Patients hypersensitive to clozapine or to any of the other excipients in ASPEN CLOZAPINE (see section 6.1).
- Patients unable to undergo regular blood tests.
- Patients with a history of toxic or idiosyncratic granulocytopenia/ agranulocytosis (with

the exception of granulocytopenia/agranulocytosis from previous chemotherapy).

- Patients with a history of ASPEN CLOZAPINE-induced agranulocytosis.
- Concomitant therapy with other medication known to suppress bone marrow function.
- Impaired bone marrow function.
- ASPEN CLOZAPINE treatment concurrently with medicines known to have a substantial potential for causing agranulocytosis. For this reason, concomitant use of depot antipsychotics is discouraged.
- Patients who present with convulsions or uncontrolled epilepsy.
- Concomitant use of ASPEN CLOZAPINE and carbamazepine.
- Alcohol psychosis or toxic psychosis, drug intoxication, comatose conditions.
- Glaucoma.
- Circulatory collapse and/or depression of the central nervous system, irrespective of the causes.
- Cardiac disorders (e.g. myocarditis) or diseases, including dysrhythmias.
- Concomitant use with medicines known to prolong the QT time.
- Severe renal disorders.
- Severe liver disorders including active liver disease associated with nausea, anorexia or jaundice; progressive liver disease and hepatic failure.
- Paralytic ileus.
- Children below the age of 16, as safety of ASPEN CLOZAPINE has not been established.
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

Agranulocytosis

ASPEN CLOZAPINE can cause agranulocytosis that may be fatal. The following precautionary

measures are therefore mandatory before prescribing ASPEN CLOZAPINE.

Because of the risks associated with ASPEN CLOZAPINE, its use is limited to patients in whom therapy is indicated (see section 4.1.)

- Patients with schizophrenia who are non-responsive to, or intolerant of antipsychotic medication, or with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1).
- Patients who initially have normal leucocyte findings (WBC count ≥ 3 500/mm^3 (3,5x10^9/L) and ANC ≥ 2 000/mm^3 (2,0x10^9/L), and
- Patients in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 2-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of ASPEN CLOZAPINE.

Before initiating ASPEN CLOZAPINE therapy, patients must have a full blood count, a history be taken, and have a thorough physical examination, including an evaluation of cardiac function and an ECG to exclude a cardiac disorder or disease.

Because of the association with agranulocytosis, ASPEN CLOZAPINE should not be used with other medicines that imply a significant risk of agranulocytosis.

ASPEN CLOZAPINE should not be used in combination with long-acting depot-antipsychotics, because these medicines may act as prolonged myelosuppressants when they cannot be removed quickly (see section 4.3).

Prior to treatment initiation, medical practitioners must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine, as contained in ASPEN CLOZAPINE, which necessitated its discontinuation.

Prescriptions for ASPEN CLOZAPINE should not be issued for periods longer than the interval between two blood counts.

Immediate discontinuation of ASPEN CLOZAPINE is **mandatory** if either the WBC count is less than 3 000/mm^3 (3,0 x10^9/L) or the ANC is less than 1 500/mm^3 (1,5x10^9/L) at any time

during ASPEN CLOZAPINE treatment. Patients in whom clozapine-containing medicines such as ASPEN CLOZAPINE have been discontinued as a result of either WBC or ANC deficiencies must never be re-exposed to ASPEN CLOZAPINE.

At each consultation, a patient receiving ASPEN CLOZAPINE must be reminded to contact the treating medical practitioner 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 and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients with a history of primary bone marrow disorders must not be treated with ASPEN CLOZAPINE (see section 4.3.).

Treatment of patients who have low WBC counts because of benign ethnic neutropenia should only be considered for treatment with ASPEN CLOZAPINE after consultation with a haematologist and if no safer alternative option is available to them.

White blood cell (WBC) counts and absolute neutrophil count (ANC) monitoring

WBC and differential blood counts must be performed within 10 days prior to initiating ASPEN CLOZAPINE treatment to ensure that only patients with normal WBC counts and ANC (WBC count ≥ 3 500/mm^3 (3,5x10^9/L) and ANC ≥ 2 000/mm^3 (2,0x10^9/L)) will receive ASPEN CLOZAPINE. After starting ASPEN CLOZAPINE treatment, regular WBC count and ANC must be performed and monitored weekly for the first 18 weeks, and at least at two-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of ASPEN CLOZAPINE or until haematological recovery has occurred (see “Low WBC count

or ANC" below). At each consultation, the patient must be reminded to contact the treating medical practitioner immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

Low WBC (White Blood cell Count) or ANC (Absolute Neutrophil Count)

Immediate discontinuation of ASPEN CLOZAPINE treatment is **mandatory** if either the WBC count is less than 3 000/mm^3 (3,0 x 10^9/L) or the ANC is less than 1 500/mm^3 (1,5 x 10^9/L) during ASPEN CLOZAPINE treatment. 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. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, ASPEN CLOZAPINE should be discontinued after the first blood count.

Following discontinuation of ASPEN CLOZAPINE, haematological evaluation is required until haematological recovery has occurred.

Table 1: Blood monitoring during ASPEN CLOZAPINE therapy

Blood cell count		**Action required**
WBC/mm^3 (/L)	**ANC/mm^3 (/L)**	
≥ 3 500 (≥ 3,5x10^9)	≥ 2 000 (≥ 2,0x10^9)	Continue ASPEN CLOZAPINE treatment.
Between ≥ 3 000 and < 3 500 (≥ 3,0x10^9 and < 3,5x10^9)	Between ≥ 1 500 and < 2 000 (≥ 1,5x10^9 and < 2,0x10^9)	Continue ASPEN CLOZAPINE treatment, sample blood twice weekly until counts stabilise or increase.
< 3 000 (< 3,0x10^9)	< 1 500 (< 1,5x10^9)	Immediately stop ASPEN CLOZAPINE treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. **Do not re-expose the patient.**

If ASPEN CLOZAPINE has been withdrawn and either a further drop in the WBC count below 2000/mm^3 (2,0x10^9/L) occurs or the ANC falls below 1000/mm^3 (1,0x10^9/L), the management of this condition must be guided by an experienced haematologist.

Discontinuation of therapy for haematological reasons

Patients in whom ASPEN CLOZAPINE has been discontinued as a result of either WBC or ANC deficiencies (see above) must not be re-exposed to ASPEN CLOZAPINE.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.

Discontinuation of therapy for other reasons

Patients who have been using ASPEN CLOZAPINE for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 2 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals of 2 weeks may be resumed.

If ASPEN CLOZAPINE treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated (see section 4.2.).

Other precautions

Eosinophilia

In the event of eosinophilia, discontinuation of ASPEN CLOZAPINE is recommended if the eosinophil count rises above 3 000/mm^3 (3,0x10^9/L); therapy should be restarted only after the eosinophil count has fallen below 1 000/mm^3 (1,0x10^9/L).

Thrombocytopenia

In the event of thrombocytopenia, discontinuation of ASPEN CLOZAPINE therapy is recommended if the platelet count falls below 50 000/mm^3 ($50x10^9$/L).

Cardiovascular disorders

Orthostatic hypotension, with or without syncope, can occur during ASPEN CLOZAPINE treatment. Cardiovascular collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of a benzodiazepine or any other psychotropic medicines and during initial titration in association with rapid dose escalation. However, they may occur even after the first dose. Therefore, patients starting ASPEN CLOZAPINE treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease (see section 4.8.).

The use of ASPEN CLOZAPINE is associated with an increased risk of myocarditis especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal (see section 4.3.).

Pericarditis/pericardial effusion and cardiomyopathy, which may be fatal, have been reported in association with ASPEN CLOZAPINE use.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, dysrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms which mimic myocardial infarction. Other symptoms may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, ASPEN CLOZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist (see section 4.8.).

Patients with cardiomyopathy while using ASPEN CLOZAPINE may develop mitral valve incompetence with mild or moderate mitral regurgitation on two-dimensional echocardiography

(2DEcho).

Patients with clozapine-induced myocarditis or cardiomyopathy should never be re-exposed to ASPEN CLOZAPINE (see section 4.8).

Myocardial infarction

There have been reports of myocardial infarction which may be fatal.

QT interval prolongation

Caution must be exercised in patients with known cardiovascular disease or family history of QT prolongation.

Caution must also be exercised when ASPEN CLOZAPINE is prescribed concomitantly with medicines known to increase QTc interval (see section 4.3. and 4.5.).

Cerebrovascular adverse events

ASPEN CLOZAPINE should be used with caution in patients with risk factors for stroke.

Risk of thromboembolism

Since ASPEN CLOZAPINE may be associated with thromboembolism, immobilisation of patients should be avoided.

All possible risk factors for VTE should be identified before and during treatment with ASPEN CLOZAPINE and preventive measures undertaken (see section 4.5).

Seizures

Patients with a history of epilepsy should be closely observed during ASPEN CLOZAPINE therapy since dose-related convulsions have been reported. In such cases, the dose should be

reduced and, if necessary, an anti-convulsant treatment should be initiated (see section 4.3.).

Anticholinergic effects

ASPEN CLOZAPINE 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, ASPEN CLOZAPINE has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation, faecal impaction, faecaloma, megacolon, paralytic ileus, intestinal obstruction, bowel perforation, and gut ischaemia which may be fatal.

Particular care should be taken in patients at risk of constipation, including those:

- receiving medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants, and antiparkinsonian treatments; as well as opioids).
- with a history of colonic disease or a history of lower abdominal surgery.
- aged 60 years and older.

Healthcare providers should counsel patients about the risk of constipation with ASPEN CLOZAPINE and question patients about their bowel movements. Healthcare providers should encourage adequate hydration, physical activity, and a high-fibre diet. Review all medicines (especially anti-cholinergic medicines and opiates) and re-assess the need. Healthcare providers should strongly encourage monitoring of bowel function by patient, family and healthcare providers.

Most importantly, it is vital that constipation is recognized early and should be actively managed. Patients should be advised to urgently contact their healthcare providers if they

develop constipation. Initiate treatment promptly if constipation is suspected or reported (see section 4.5. and 4.8.).

Fever

During ASPEN CLOZAPINE therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever 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. If the diagnosis of NMS is confirmed, ASPEN CLOZAPINE should be discontinued immediately, and appropriate treatment should be initiated.

Metabolic changes

Atypical antipsychotic medicines, including ASPEN CLOZAPINE, have been associated with metabolic changes which may increase the risk of cardiovascular/cerebrovascular adverse effects. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain.

Hyperglycaemia

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported during treatment with clozapine, as contained in ASPEN CLOZAPINE. A mechanism for this possible association has not been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported in patients with no prior history of hyperglycaemia, some of which have been fatal. Discontinuation of clozapine, as in ASPEN CLOZAPINE, resulted mostly in resolution of the impaired glucose tolerance, and reinstitution

of clozapine, as in ASPEN CLOZAPINE, resulted in its reoccurrence (see BOXED WARNING 4).

Patients with an established diagnosis of diabetes mellitus who are started on ASPEN CLOZAPINE 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 ASPEN CLOZAPINE should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

Patients who develop symptoms of hyperglycaemia during treatment with ASPEN CLOZAPINE should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved after ASPEN CLOZAPINE was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of ASPEN CLOZAPINE. The discontinuation of ASPEN CLOZAPINE should be considered in patients where active medical management of their hyperglycaemia has failed.

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including ASPEN CLOZAPINE.

Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using ASPEN CLOZAPINE, is recommended.

Weight gain

Weight gain has occurred with atypical antipsychotic use, including ASPEN CLOZAPINE.

Clinical monitoring of weight is recommended.

Rebound, withdrawal effects

Acute withdrawal reactions have been reported following abrupt cessation of ASPEN CLOZAPINE therefore gradual withdrawal is recommended.

If abrupt discontinuation is necessary (e.g. because of leucopoenia), 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.

Special populations

Hepatic impairment

Patients with stable pre-existing liver disorders may receive ASPEN CLOZAPINE but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting and/or anorexia, develop during ASPEN CLOZAPINE therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL (Upper Normal Limit)) or if symptoms of jaundice occur, treatment with ASPEN CLOZAPINE must be discontinued. It may be resumed only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of ASPEN CLOZAPINE (see section 4.3.).

Patients aged 60 years and older

Initiation of treatment in patients aged 60 years and older is recommended at a lower dose (see section 4.2.).

Orthostatic hypotension can occur with ASPEN CLOZAPINE treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects. Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of ASPEN CLOZAPINE, such as urinary retention and constipation.

Increased mortality in elderly people with dementia

ASPEN CLOZAPINE is not indicated for the treatment of dementia-related behavioural disturbances.

Excipients

ASPEN CLOZAPINE 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 should not take ASPEN CLOZAPINE.

4.5. Interaction with other medicines and other forms of interaction

- Opioid medicines such as codeine, oxycodone and morphine must not be used concurrently with ASPEN CLOZAPINE as these may cause constipation, leading to fatal hypomotility (see BOXED WARNING 6)
- Medicines known to have a substantial potential to depress bone marrow function must not be used concurrently with ASPEN CLOZAPINE (see section 4.3).
- ASPEN CLOZAPINE should not be used in combination with medication which can potentially be myelosuppressive, because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia (see section 4.3 and 4.4).
- ASPEN CLOZAPINE may increase the central nervous system (CNS)-depressive effects of alcohol, monoamine oxidase (MAO)-inhibitors, and other CNS-depressive medicines such as narcotics, antihistamines and benzodiazepines.
- Alcohol should not be used concomitantly with ASPEN CLOZAPINE due to possible potentiation of sedation.
- Concurrent use with carbamazepine may increase the risk of severe haematological

effects (see section 4.3.).

- Concurrent or recent treatment with benzodiazepines or other psychotropic medicines increases the risk of circulatory collapse with respiratory depression or arrest (see section 4.4).
- 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 (see section 4.4.).
- Owing to its anti-alpha-adrenergic properties, ASPEN CLOZAPINE may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic medicines and reverse the pressor effect of epinephrine.
- Serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where ASPEN CLOZAPINE was co-administered with valproic acid have been reported (see section 4.8.).
- ASPEN CLOZAPINE 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.
- Concomitant administration of medicines known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of ASPEN CLOZAPINE, and the dose of ASPEN CLOZAPINE may need to be reduced to prevent undesirable effects.
    - Medicines known to inhibit the activity of the major isozymes involved in the metabolism of ASPEN CLOZAPINE and with reported interactions include cimetidine, erythromycin (3A4), fluvoxamine (1A2), sertraline, fluoxetine, citalopram and paroxetine.
    - Potent inhibitors of CYP3A, such as azole antifungals and protease inhibitors, may increase clozapine plasma concentrations.
    - Elevated clozapine plasma concentrations have been reported in patients

receiving ASPEN CLOZAPINE in combination with selective serotonin re-uptake inhibitors such as paroxetine (1A2), sertraline, fluoxetine, citalopram or fluvoxamine (see Table 2).

- This is more important for CYP 1A2 inhibitors such as caffeine, perazine and the selective serotonin reuptake inhibitor, fluvoxamine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, sertraline, are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely.
- Hormonal contraceptives (including combinations of oestrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of ASPEN CLOZAPINE according to the individual medical need.

  Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50 % following a 5-day caffeine-free period, dosage changes of ASPEN CLOZAPINE may be necessary when there is a change in caffeine intake.

  In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects (see Table 2).
- Concomitant administration of medicines known to induce cytochrome P450 enzymes may decrease the plasma levels of ASPEN CLOZAPINE and may be associated with the recurrence of psychotic symptoms:
  - Substances known to induce the activity of cytochrome P450 enzymes and with reported interactions with ASPEN CLOZAPINE include, carbamazepine, phenytoin and rifampicin (see section 4.3).
  - Known inducers of 1A2 include omeprazole and nicotine. In cases of sudden cessation of nicotine use, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

- Competition of binding sites on plasma proteins can lead to changes in plasma levels of ASPEN CLOZAPINE or other medicines which bind strongly to protein e.g. warfarin. Concurrent administration of ASPEN CLOZAPINE with erythromycin or cimetidine may increase plasma levels of ASPEN CLOZAPINE.
- The concurrent use of ASPEN CLOZAPINE and lithium or other CNS-active medicines increase the risk of neuroleptic malignant syndrome.

Table 2: Reference to the most common medicine interactions with ASPEN CLOZAPINE

Medicine	Interactions	Comments
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic medicines and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	ASPEN CLOZAPINE must not be used concomitantly with other medicines having a well-known potential to suppress bone marrow function (see section 4.3.)
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest	Caution is advised when using these medicines together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when ASPEN CLOZAPINE is added to an established benzodiazepine regimen.
Anticholinergics	ASPEN CLOZAPINE potentiates the action of these medicines through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help

		control hypersalivation.
Antihypertensives	ASPEN CLOZAPINE can potentiate the hypotensive effects of these medicines due to its sympathomimetic antagonistic effects.	Caution is advised if ASPEN CLOZAPINE is used concomitantly with antihypertensive medicines. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs (including linezolid), CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these medicines/substances.	Caution is advised if ASPEN CLOZAPINE is used concomitantly with other CNS active medicines/substances. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g. warfarin and digoxin)	ASPEN CLOZAPINE may cause an increase in plasma concentration of these medicines due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these medicines, and doses of the protein bound medicine adjusted, if necessary.
Phenytoin	Addition of phenytoin to ASPEN CLOZAPINE regimen may cause a decrease in clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing	Concomitant use may	Potential for reduced

substances (e.g. omeprazole)	decrease clozapine levels.	efficacy of ASPEN CLOZAPINE should be considered.
CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, pyrazine or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels.	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medicines as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.

4.6. Fertility, pregnancy and lactation

Safety of ASPEN CLOZAPINE in pregnancy and lactation has not been established.

ASPEN CLOZAPINE should not be used during pregnancy and lactation (see section 4.3.).

Women of childbearing potential / Contraception in males and females

A return to normal menstruation may occur as a result of switching from other antipsychotics to ASPEN CLOZAPINE. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Pregnancy

Neonates exposed to antipsychotics, including ASPEN CLOZAPINE, during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms which may vary in severity and duration following delivery.

There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, new-borns should be monitored carefully.

Breastfeeding

Mothers receiving ASPEN CLOZAPINE should not breastfeed their babies.

4.7. Effects on ability to drive and use machines

Since adverse reactions such as blurred vision, dizziness and drowsiness have been reported in patients receiving ASPEN CLOZAPINE, patients should not drive, use machinery or perform any tasks which require concentration, until they are certain that ASPEN CLOZAPINE does not adversely affect their ability to do so (see section 4.8.).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations			Sepsis
Blood and the lymphatic system disorders	Leucopenia/decreased WBC/neutropenia, eosinophilia, leucocytosis	Agranulocytosis, anaemia	Thrombocytopenia, thrombocythaemia
Immune system disorders			Angioedema, leucocytoclastic vasculitis
Endocrine disorders			Pseudophaeochromocytoma
Metabolism and nutrition disorders	Weight gain	Diabetes mellitus, impaired glucose tolerance, hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia, elevation of creatine phosphokinase (CPK)	
Psychiatric disorders	Dysarthria, confusion, delirium	Agitation, dysphaemia, restlessness	
Nervous system disorders	Drowsiness, sedation, thermoregulatory disorders	Dizziness, headaches, neuroleptic malignant syndrome, extrapyramidal effects, rigidity, tremor and akathisia, tardive	Cholinergic syndrome (after abrupt withdrawal), pleurothotonus

		dyskinesia. ASPEN CLOZAPINE 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 medicines, the possibility of a pharmacokinetic interaction should be considered.	
Eye disorders	Blurred vision, accommodation disorders		
Cardiac disorders	Tachycardia, ECG changes	Cardiomyopathy, cardiac arrest, circulatory collapse, dysrhythmia, myocarditis with or without eosinophilia, pericarditis/ pericardial effusion which may be fatal, orthostatic hypotension, with or without syncope, especially in the initial weeks of treatment.	Myocardial infarction which may be fatal, chest pain/angina pectoris, atrial fibrillation, palpitations, mitral valve incompetence associated with clozapine related cardiomyopathy
Vascular disorders	Syncope, postural hypotension, hypertension	Circulatory collapse accompanied by respiratory depression or arrest. Venous and pulmonary thromboembolism. Electrocardiogram (ECG) changes may occur and cases of cardiac dysrhythmias, pericarditis and myocarditis (with or without eosinophilia), in some cases fatal	Hypotension
Respiratory, thoracic and mediastinal disorders		Aspiration of ingested food, as a consequence of dysphagia, pneumonia and lower respiratory tract infection which may be fatal,	Nasal congestion

		respiratory depression/arrest	
Gastrointestinal disorders	Anorexia, dry mouth, nausea, vomiting and constipation, hypersalivation,	Dysphagia, intestinal obstruction/paralytic ileus/faecal impaction, parotid gland enlargement, faecaloma, megacolon, bowel perforation, bowel ischaemia	Diarrhoea, abdominal discomfort/ heartburn/ dyspepsia, colitis
Hepato-biliary disorders	Asymptomatic elevations in liver enzymes	Fulminant hepatic necrosis, hepatitis, cholestatic jaundice and acute pancreatitis	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		Skin reactions	Pigmentation disorder
Musculoskeletal and connective tissue disorders			Muscle weakness, muscle spasms, muscle pain, systemic lupus erythematosus (SLE)
Renal and urinary disorders		Urinary incontinence, urinary retention and interstitial nephritis.	Renal failure, nocturnal enuresis
Pregnancy, puerperium and perinatal conditions			Neonatal drug withdrawal syndrome
Reproductive system and breast disorders	Priapism		Retrograde ejaculation
General disorders and administrative site conditions	After long-term treatment considerable weight gain has occurred, benign hyperthermia, disturbances in sweating/temperature regulation, fever, fatigue	Sudden and unexplained death	
Investigations		Increased CPK	

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. Health care provders 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:

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

Aspen Pharmacare:
E-mail: Drugsafety@aspenpharma.com
Tel: 0800 118 088

4.9. Overdose

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

Symptoms

In overdose, side effects will be elicited and exacerbated (see section 4.8).

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 dysrhythmias, aspiration, pneumonia, dyspnoea, heart block, respiratory depression or failure.

Treatment

Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic and supportive treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance.

Close medical supervision is necessary for several days because of the possibility of delayed reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: A 2.6.5 Tranquillizer (miscellaneous structures).

ATC code: Antipshychotics, N05AH02

Mechanism of action

Clozapine is an atypical antipsychotic medicine. 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

Absorption

The absorption of orally administered clozapine is 90 % to 95 % and independent of food intake. Clozapine is subject to moderate first-pass metabolism and has an absolute bioavailability of approximately 50 % to 60 %.

Distribution

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 1,8 ± 1,1 L/kg. The plasma protein binding is approximately 95 %. The elimination is biphasic with a mean terminal half-life of 12 hours.

Biotransformation

Clozapine is almost completely metabolised 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.

Elimination

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

Lactose monohydrate, magnesium stearate, maize starch, povidone K30, purified talc and silica colloidal anhydrous.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store in a dry place at or below 25°C

Protect from moisture and light.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

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.

6.6. Special precautions for disposal

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodmead 2191

8. REGISTRATION NUMBER

ASPEN CLOZAPINE 25 mg: 38/2.6.5/0167

ASPEN CLOZAPINE 100 mg: 38/2.6.5/0168

9. DATE OF FIRST AUTHORISATION

Date of registration: 23 November 2005

10. DATE OF REVISION OF TEXT

Date of the most recent amendment to the professional information as approved by the Authority: 27 May 2020

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