

VI.2 Elements for a Public Summary**VI.2.1 Overview of disease epidemiology****Schizophrenia (a type of mental disorders)**

Schizophrenia is a long-term mental health condition that causes a range of different psychological symptoms. The occurrence of schizophrenia is 15.2/100,000 persons worldwide. The rate ratio for males:females is 1.4:1. Prevalence (total present numbers) estimates also show prominent variation. The lifetime morbid (caused by disease) risk for schizophrenia is 7.2/1,000 persons. On the basis of the standardized mortality (death on large scale) ratio, people with schizophrenia have a two to three fold increased risk of dying, and this differential gap in mortality has increased over recent decades. Although suicide contributes to the increased mortality associated with schizophrenia, individuals with schizophrenia have increased mortality risks due to a wide range of comorbid (medical condition that co-occurs with other) conditions. Compared with native-born individuals, migrants have an increased occurrence and prevalence of schizophrenia. Exposures related to urbanicity, economic status, and latitude are also associated with various frequency measures.

Psychosis in Parkinson's disease (severe disturbances in the thoughts, emotions and behaviour of people with Parkinson's disease):

Psychotic symptoms are frequent and disabling in patients with Parkinson's disease (PD). Visual hallucinations (illusory visual perception) are present in about one quarter to one third of the patients, auditory (perceiving sounds without stimulus) in up to 20%. Tactile/somatic and olfactory hallucinations (smell related false perception) are usually not systematically sought. Minor phenomena such as sense of presence and visual illusions affect 17 to 72% of the patients, and delusions (A false belief or opinion) about 5%. Lifetime prevalence of visual hallucinations reaches approximately 50%. The main endogenous non-modifiable risk factor is memory impairment. Other associated factors include older age/longer duration of PD, disease severity, altered dream phenomena, daytime sleepiness, and possibly depression. PD

reduces quality of life in patients and increases caregiver distress, and is an independent risk factor for nursing home placement and development of forgetfulness.

VI.2.2 Summary of treatment benefits

Clozapine tablets contain the active substance clozapine. This medicine belongs to a group of medicines called antipsychotics (medicines that are used to treat specific mental disorders such as psychosis).

Clozapine tablets are used to treat people with schizophrenia in whom other medicines have not worked. Schizophrenia is a mental illness which affects how you think, feel and behave. You should only use this medicine if you have already tried at least two other medicines to treat schizophrenia before, and these medicines did not work, or caused severe side effects that cannot be treated.

Clozapine tablets are also used to treat severe disturbances in the thoughts, emotions and behaviour of people with Parkinson's disease in whom other medicines have not worked.

Clinically Clozapine produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, Clozapine has proven effective in relieving schizophrenic symptoms mainly in short-term trials. In an open clinical study performed in 319 treatment resistant patients treated for 12 months, a clinically relevant improvement was observed in 37% of patients within the first week of treatment and in an additional 44% by the end of 12 months.

Accord has not conducted any studies for clozapine on expected benefit considering its similarity to the currently marketed product.

VI.2.3 Unknowns relating to treatment benefits

No paediatric studies have been performed. The safety and efficacy of clozapine in children and adolescents under the age of 16 years have not yet been established. It should not be used in this group until further data become available.

For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
<p>Agranulocytosis (no white blood cells, the part of the blood that fights infection)</p>	<p>This medicine 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.</p> <p>Before you start taking Clozapine tablets, your doctor or pharmacist will ask about your medical history and do a blood test to ensure that your white blood cells count is normal. It is important to find this out, as your body needs white blood cells to fight infections.</p> <ul style="list-style-type: none"> • During the first 18 weeks of treatment, tests are 	<p>Do not take Clozapine together with below medicines that stop the bone marrow from working properly and/or decrease the number of blood cells produced by the body:</p> <p>Carbamazepine: a medicine used in epilepsy.</p> <p>Certain antibiotics: chloramphenicol, sulphonamides such as co-trimoxazole.</p> <p>Certain painkillers: pyrazolone analgesics such as phenylbutazone.</p> <p>Penicillamine, a medicine used to treat rheumatic joint</p>

Risk	What is known	Preventability
	<p>needed once a week. Afterwards, tests are needed at least once a month.</p> <ul style="list-style-type: none"> • If there is a decrease in the number of white blood cells, you will have to stop 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 clozapine treatment. <p>Uncommon side effects (may affect up to 1 in 100 people): Lack of white blood cells (agranulocytosis)</p>	<p>inflammation.</p> <p>Cytotoxic agents, medicines used in chemotherapy.</p> <p>Long-acting depot injections of antipsychotic medicines.</p> <p>Before you start taking this medicine, your doctor will ask about your medical history and do a blood test to ensure that your white blood cells count is normal. It is important to find this out, as your body needs white blood cells to fight infections.</p> <p>Tell your doctor immediately before taking clozapine if you get signs of a cold, fever, flu-like symptoms, sore throat or any other infection.</p> <p>These medicines increase your risk of developing agranulocytosis (lack of white blood cells).</p> <p>Do not take Clozapine</p> <ul style="list-style-type: none"> – If you have ever been told you have a low

Risk	What is known	Preventability
		<p>white blood cell count (e.g. leucopenia 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.</p> <ul style="list-style-type: none"> - If you had to stop using Clozapine previously because of severe side effects (e.g. agranulocytosis or heart problems). - If you use any medicine that reduces the number of white cells in your blood
Epilepsy/Seizures	This medicine might cause tiredness, drowsiness and seizures, especially at the beginning of treatment. You should not drive or operate machines while you have	<p>Do not take Clozapine:</p> <p>If you suffer from uncontrolled epilepsy (seizures or fits).</p> <p>Before you start treatment with clozapine, tell your</p>

Risk	What is known	Preventability
	<p>these symptoms.</p> <p>Increased side effects (in particular seizures) are possible at daily doses over 450 mg.</p> <p>The symptoms of overdose are:</p> <p>Drowsiness, tiredness, lack of energy, unconsciousness, coma, confusion, hallucinations, agitation, incoherent speech, stiff limbs, trembling hands, seizures (fits), increased production of saliva, widening of the black part of the eye, blurred vision, low blood pressure, collapse, fast or irregular heart beat, shallow or difficult breathing.</p> <p>If you received clozapine, seizure is a common side effects (may affect up to 1 in 10 people).</p>	<p>doctor if you suffer from or have ever suffered from controlled epilepsy and seizures.</p>
<p>Cardiovascluar disorders (Problems related to heart</p>	<p>Orthostatic hypotension</p> <p>Orthostatic hypotension can</p>	<p>Tell your doctor or pharmacist if you are taking</p>

Risk	What is known	Preventability
<p>and blood vessels) including Orthostatic (caused by an upright posture) hypotension(abnormally low blood pressure)</p> <p>Myocarditis (inflammation of the heart muscle) and Cardiomyopathy (disorder of the heart muscle)</p> <p>Pericarditis (inflammation of the lining surrounding the heart muscle)/Pericardial Effusion (fluid collection around the heart)</p> <p>Myocardial infarction (Heart attack)</p> <p>Thromboembolism (a clump of blood called a blood clot from another part of the body that blocks a blood vessel such as a vein or artery)</p> <p>Circulatory collapse (a general or specific failure of the circulation, either cardiac or peripheral in nature.)</p>	<p>occur during clozapine treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest (stopping of the heart). Such events are more likely to occur with concurrent use of medicines such as benzodiazepine (drugs used to for treating anxiety) or any other psychotropic agent (mood altering) and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease (Disorder of the central nervous system, seen usually in older persons, in which there is muscle weakness,</p>	<p>any of the following medicines:</p> <p>Medicines used to treat high or low blood pressure such as adrenaline and noradrenaline.</p> <p>Increases in the dosage should be stopped or postponed if you feel faint, light-headed or confused. In order to avoid such symptoms your blood pressure will be measured during the first weeks of treatment.</p> <p>Do not take Clozapine</p> <p>If you suffer from myocarditis (an inflammation of the heart muscle).</p> <p>Tell your doctor immediately:</p> <p>If you experience any signs and symptoms of cardiomyopathy (disorder of the heart muscle).</p> <p>Before taking the next Clozapine if you have fast</p>

Risk	What is known	Preventability
	<p>trembling, sweating)</p> <p>Myocarditis and Cardiomyopathy:</p> <p>The use of 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.</p> <p>Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia (Fast heart beat) at rest, especially in the first two months of treatment, and/or palpitations (heart not beating regularly), arrhythmias (Any change from the normal heart beat), chest pain and other signs and symptoms of heart failure [(e.g. unexplained fatigue, dyspnoea (Trouble breathing), tachypnoea (Fast</p>	<p>and irregular heart beat, even when you are at rest, palpitations, breathing problems, chest pain or unexplained tiredness.</p> <p>Your doctor will need to check your heart and if necessary refer you to a cardiologist immediately</p> <p>Patients with clozapine-induced cardiomyopathy (disorder of the heart muscle) should not be re-exposed to clozapine.</p> <p>Tell your doctor immediately if you experience any signs and symptoms of pericarditis/pericardial effusion.</p> <p>Before you start treatment with Clozapine, tell your doctor or pharmacist if you suffer from or have ever suffered from: heart attacks that may lead to death have been reported with</p>

Risk	What is known	Preventability
	<p>breathing), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist.</p> <p>Eosinophilia (an increase in the number of eosinophils in the blood) has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis (Inflammation of the membrane surrounding the heart muscle) /pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis (inflammation of the heart).</p> <p>Rare side</p>	<p>Clozapine.</p> <p>Tell your doctor immediately before taking the next Clozapine if you experience crushing chest pain, sensation of chest tightness, pressure or squeezing (chest pain may radiate to the left arm, jaw, neck and upper abdomen), shortness of breath, sweating, weakness, light headedness, nausea, vomiting and palpitations (symptoms of heart attack). You should seek emergency medical treatment immediately.</p> <p>Tell your doctor or pharmacist if you experience any symptoms of thromboembolism or circulatory collapse.</p> <p>Do not take Clozapine: If you suffer from circulatory collapse which may occur as a result of severe shock.</p>

Risk	What is known	Preventability
	<p>effects:inflammation of the heart muscle (myocarditis)</p> <p>Cardiomyopathy (disorder of the heart muscle) is very rare (may affect up to 1 in 10,000 people):disorder of the heart muscle (cardiomyopathy)</p> <p>Pericarditis:</p> <p>Eosinophilia (an increase in the number of eosinophils in the blood) has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis (Inflammation of the membrane surrounding the heart muscle) /pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis (inflammation of the heart).</p> <p>Inflammation of the</p>	

Risk	What is known	Preventability
	<p>membrane surrounding the heart muscle (pericarditis) is a rare side effects (may affect up to 1 in 1,000 people)</p> <p>Myocardial infarction:</p> <p>In unknown number of patients following side effects have been reported: crushing chest pain, sensation of chest tightness, pressure or squeezing (chest pain may radiate to the left arm, jaw, neck and upper abdomen), shortness of breath, sweating, weakness, light headedness, nausea, vomiting and palpitations (symptoms of heart attack).</p> <p>Thromboembolism</p> <p>Side effects of</p> <p>Blood clot in the lungs (thromboembolism) have been reported rarely which may affect up to 1 in 1,000 people.</p>	

Risk	What is known	Preventability
	<p>Circulatory collapse:</p> <p>It is a rare side effect which may affect up to 1 in 1,000 people.</p>	
<p>Anticholinergic effects (blocking the action of the chemical messenger acetylcholine in the central and the peripheral nervous system.)</p>	<p>Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the patients with prostatic problems and glaucoma (increased pressure in the eye). Probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of impairment of large intestinal, ranging from constipation to intestinal obstruction, faecal impaction (solid, immobile bulk of human feces that can develop in the rectum as a result of long term constipation) and paralytic ileus (intestines, or</p>	<p>Before you start treatment with Clozapine, tell your doctor or pharmacist if you suffer from or have ever suffered from: chronic constipation or if you are taking medicines which cause constipation (such as anticholinergics).</p> <p>Tell your doctor or pharmacist if you are taking any of the following medicines: anticholinergic medicines, which are used to relieve stomach cramps, spasms and travel sickness.</p>

Risk	What is known	Preventability
	<p>bowels, working more slowly because of they are blocked). Constipation is a very common side effect may affect more than 1 in 10 people.</p> <p>Severe constipation with abdominal pain and stomach cramps caused by obstruction of the bowel (paralytic ileus), swollen abdomen, abdominal pain are very rare side effect which may affect up to 1 in 10,000 people.</p>	
<p>Metabolic disorders including {Hyperglycaemia (high blood sugar)</p> <p>Dyslipidemia (abnormal amount of lipids)</p> <p>Weight gain}</p>	<p>Hyperglycemia (high blood sugar)</p> <p>Rare side effects (may affect up to 1 in 1,000 people):high level of sugar in the blood, diabetes mellitus</p> <p>Dyslipidemia (abnormal amount of lipids):</p> <p>This medicine very rarely may cause alteration in blood lipids.</p> <p>Weight gain:</p>	<p>Before you start treatment with Clozapine, tell your doctor or pharmacist if you suffer from or have ever suffered from: diabetes. Elevated (sometimes considerably) blood sugar levels, has occurred in patients with or without diabetes mellitus in their medical history.</p> <p>Tell your doctor immediately if you experience any signs</p>

Risk	What is known	Preventability
	<p>This medicine may cause weight gain.</p> <p>It is a common side effect which may affect up to 1 in 10 people.</p>	<p>or symptoms of dyslipidemia</p> <p>Your doctor may regularly monitor your weight, blood lipid levels and weight.</p>
<p>Acute withdrawal reactions</p>	<p>Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal is recommended.</p> <p>Do not stop taking Clozapine without asking your doctor, because you might get withdrawal reactions. These reactions include sweating, headache, nausea (feeling sick), vomiting (being sick) and diarrhoea. Your original symptoms might come back. Your doctor will advise you on how to reduce your daily dose. If you have to stop Clozapine treatment suddenly, your will have to be checked by your doctor.</p>	<p>Tell you doctor or pharmacist immediately if you experience any signs or symptoms of acute withdrawal reactions</p>
<p>Fulminant hepatic necrosis</p>	<p>Very rare side effects (may</p>	<p>Tell your doctor or</p>

Risk	What is known	Preventability
(severe liver damage)	<p>affect up to 1 in 10,000 people): severe liver damage (fulminant hepatic necrosis)</p> <p>Inflammation of the liver (hepatitis), nausea (feeling sick), vomiting (being sick) and/or loss of appetite are rare side effects which may affect up to 1 in 1,000 people.</p> <p>Not known (frequency cannot be estimated from the available data):</p> <p>Liver disorders including fatty liver disease, death of liver cells, liver toxicity/injury, liver disorders that involve replacement of normal liver tissue with scar tissue leading to loss of liver function, including those liver events leading to life-threatening consequences such as liver failure (which may lead to death), liver injury (injury of liver cells, bile duct in the liver, or both)</p>	<p>pharmacist if you experience any signs or symptoms of fulminant hepatic necrosis</p> <p>Do not take clozapine</p> <ul style="list-style-type: none"> - If you have symptoms of active liver disease such as jaundice (yellow colouring of the skin and eyes, feeling sick and loss of appetite). - If you suffer from any other severe liver disease. <p>Before you start treatment with clozapine, tell your doctor if you suffer from or have ever suffered from liver disease.</p> <p>If you have a liver disorder you will have regular liver function tests as long as you continue to take this medicine.</p>

Risk	What is known	Preventability
	and liver transplant,	
Neuroleptic malignant syndrome [(rare but potentially life-threatening peculiar reaction (abnormal reaction) to neuroleptic, Antidepressants or Antipsychotic drugs)]	Uncommon side effects (may affect up to 1 in 100 people): neuroleptic malignant syndrome.	Tell your doctor or pharmacist immediately before taking the next Clozapine: If you have 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.
Hypersensitivity (Over sensitivity/strong reaction)	Clozapine can cause hypersensitivity (Over sensitivity/strong reaction) to the patients who are allergic to clozapine or its excipients. Frequency not Known: allergic reaction (swelling mainly of the face, mouth and throat, as well as, the tongue, which may be itchy or painful)	Do not take if you are allergic (hypersensitive) to clozapine or any of the other ingredients of this medicine. Tell your doctor if you plan to take, if you are taking or if you have recently stopped taking antihistamines, medicines used for colds or allergies such as hay fever (inflammation of nose due to allergy).
Excessive Sedation	Excessive Sedation	Cautious titration and a

Risk	What is known	Preventability
<p>(excessively promoting calm or inducing sleep)</p>	<p>(excessively promoting calm or inducing sleep) is the most common side effect.</p> <p>In young children, the intake of 50 to 200 mg resulted in strong sedation (promoting calm or inducing sleep) or coma without being lethal (very harmful/destructive)</p>	<p>divided dosage schedule are necessary to minimise the risks of sedation (promoting calm or inducing sleep)</p> <p>Dose increases should be limited or deferred if excessive sedation (promoting calm or inducing sleep) or confusion occurs.</p> <p>Alcohol should not be used concomitantly (at the same time) with clozapine due to possible potentiation of sedation (promoting calm or inducing sleep).</p> <p>Caution is advised if clozapine is used concomitantly (at the same time) with other CNS active agents (drugs acting on brain and spinal cord).</p> <p>Patients should be advised for the possible additive sedative effects (promoting calm or inducing sleep) and caution them not to drive or operate machinery.</p>

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
<p>Cerebrovascular (relating to the brain and its blood vessels) adverse events and increased risk of death in elderly patients with dementia (a chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning) related psychosis.</p>	<p>An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics (type of drugs). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Clozapine tablets should be used with caution in patients with risk factors for stroke.</p> <p>Observational studies (type of research draws a conclusion by comparing subjects against a control group, in cases where the researcher has no control over the experiment) showed that patients aged 60 years and older with dementia (a chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning)-related psychosis treated with antipsychotic drugs (tranquilizer) are at a small increased risk of death compared with those who are not treated.</p>
<p>Sudden unexplained death</p>	<p>Very rarely, side effects like sudden unexplained death have been reported which may affect up to 1 in 10,000 people.</p>
<p>Renal (kidney) failure</p>	<p>Frequency not known:</p> <p>Experience of severely decreased urine output (sign of</p>

Risk	What is known (Including reason why it is considered a potential risk)
	<p>kidney failure)</p> <p>Do not take this medicine; if you are suffering from any severe kidney disease.</p> <p>Tell your doctor immediately before taking the next Clozapine: If you experience severely decreased urine output (sign of kidney failure).</p> <p>Unknown number of patients experienced side effects of Severely decreased urine output (sign of kidney failure)</p>
<p>Interaction with drugs which are either inhibitor or inducer of CYP450{(type of enzymes) isoenzymes (including antiepileptics like phenytoin) (drug used to prevent seizures)}</p>	<p>Caution is called for in patients receiving concomitant treatment with other substances which are either inhibitors or inducers of the cytochrome P450 isozymes.</p> <p>Concomitant (Given at the same time) administration of substances known to induce cytochrome P450 enzymes may decrease the blood levels of clozapine, leading to reduced efficacy.</p> <p>Concomitant (Given at the same time) administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the blood levels of clozapine.</p> <p>Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or herbal therapies. You might need to take different amounts of your medicines or to take different medicines.</p> <p>Rare but serious reports of seizures (fits), including onset of</p>

Risk	What is known (Including reason why it is considered a potential risk)
	<p>seizures in non-epileptic (without fits) patients, have been reported.</p> <p>Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations (blood concentration)</p> <p>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 clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.</p>
Interaction with valproic acid (an antiepileptic drug)	<p>Isolated cases of delirium (A state of mental confusion and fluctuating consciousness) where clozapine was co-administered with valproic acid have been reported.</p> <p>Ask your doctor if you plan to take, if you are taking (even if the course of treatment is about to end) or if you have recently had to stop taking any medicine used to control epilepsy such valproic acid.</p>
Interaction with citalopram (an antidepressant drug)	<p>Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully understood.</p>
Drug withdrawal syndrome	<p>The following symptoms may occur in newborn babies, of</p>

Risk	What is known (Including reason why it is considered a potential risk)
neonatal (new born child)	mothers that have used clozapine in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
Interaction with highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause an increase in plasma concentration of warfarin and digoxin due to displacement from plasma proteins. Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.

Missing information

Risk	What is known
Use in children and adolescent under age of 16	If you are under 16 years of age you should not use clozapine as there is not enough information on its use in that age group.
Use in pregnant and lactating population	If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the benefits and possible risks of using this medicine during pregnancy. Tell your doctor or pharmacist immediately if you become pregnant during treatment with clozapine.

	<p>The following symptoms may occur in newborn babies, of mothers that have used clozapine in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.</p> <p>Some women taking some medicines to treat mental illness have irregular or no periods. If you have been affected in this way, your periods may return when your medicine is changed to clozapine. This means you should use effective contraception.</p> <p>Do not breast-feed during treatment with this medicine. Clozapine, the active substance of clozapine, may pass into your milk and affect your baby.</p>
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VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Need for education material as an additional risk minimisation measure will be discussed with national competent authority before launch. If required, the content will be alligned with the reference product education material.

Agranulocytosis, Myocarditis and Cardiomyopathy

Healthcare Professional/Patient education
Objective and rationale: Patients and HCPs to understand the risk of occurrence of Agranulocytosis, Myocarditis and Cardiomyopathy and the appropriate management of this risk to minimise its occurrence and its severity.
Proposed action: HCP and Patient educational materials to be provided to prescribing physicians, pharmacists and patients including advice on: <ul style="list-style-type: none"> • Starting Clozapine in a Patient • Maintenance of patient on Clozapine • Frequency of Monitoring WBC and ANC • Information on an increased risk of myocarditis with clozapine and its management

Initiation of clozapine treatment must be restricted to those patients with a WBC count $\geq 3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$) and an ANC $\geq 2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$) within standardized normal limits.

Because of this risk, its use is restricted to treatment resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed only for 25, 50 and 100 mg tablets.

VI.2.6 Planned post authorisation development plan

None

VI.2.7 Summary of changes to the Risk Management Plan over time