

## **VI.2 Elements for a Public Summary**

### **VI.2.1 Overview of disease epidemiology**

Schizophrenia is a disabling mental illness with a lifetime prevalence of 0.7% worldwide and significant, often devastating, consequences on social and occupational functioning. High incidence figures have recently been reported in some disadvantaged social groups, especially ethnic minorities in Western Europe, such as Afro-Caribbean communities in the United Kingdom and immigrants from Surinam in the Netherlands. Point prevalence on adults ranges between 1 and 17 per 1000 population, one-year prevalence between 1 and 7.5 per 1000, and lifetime prevalence between 1 and 18 per 1000. Variations in prevalence can be related to several factors, including differences in recovery, death and migration rates among the affected individuals. The number of people with schizophrenia around the world can be estimated at about 29 million, of whom 20 million live in developing or least developed countries.

### **VI.2.2 Summary of treatment benefits**

Clozapine is 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. Clozapine is 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.

In a clinical trial performed in 319 treatment-resistant patients treated for 12 months, a clinically relevant improvement was observed in 37% of patients (118 patients) within the first week of treatment and in an additional 44% (140 patients) by the end of 12 months. In addition, improvement in some aspects of cognitive dysfunction has been described.

## **Risk Management Plan [Clozapine] Version 2.0**

Compared to classic psychiatric medicines, clozapine produces fewer major uncontrollable movement reactions such as acute uncontrollable muscle spasms, parkinsonian-like side effects and restlessness or difficulty sitting still. In contrast to classic psychiatric medicines, clozapine produces little or no prolactin (a hormone) elevation, thus avoiding adverse effects such as breast enlargement in men, abnormal absent menstrual periods, unusual secretion of breast milk and an inability to get or maintain an erection.

The study mentioned above was conducted for Clozaril® by Novartis Pharmaceuticals UK Ltd, and not by Mylan.

### **VI.2.3 Unknowns relating to treatment benefits**

#### *Paediatric population*

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.

#### Use in pregnancy

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.

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

#### Use in lactating women

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving clozapine should not breast-feed.

### **VI.2.4 Summary of safety concerns**

*Table 32 Part VI - Summary table of safety concern*

#### **Important identified risk**

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
<p>Severe reduction in number of white blood cells which makes infections more likely (agranulocytosis)</p>	<p>Patients who have ever been told that they have a low white blood cell count should not take this medicine, especially if this was caused by medicines. Patients who have had to stop using clozapine before because they have experienced agranulocytosis should not take this medicine. Patients should have regular blood tests before, during and after treatment to monitor white blood cell counts. Patients should not take clozapine with medicines that stop the bone marrow from working properly and/or decrease the number of blood cells produced by the body as such medicines increase the risk of developing agranulocytosis.</p>	<p>Clozapine should not be given to patients who have previously experienced low white blood cell counts, especially if this was caused by medicines. Clozapine should not be given to patients who have previously had to stop using the drug as they have experienced agranulocytosis. Patients should have regular blood tests before, during and after treatment to monitor white blood cell counts. Patients should be informed not to take clozapine with medicines that stop the bone marrow from working properly and/or decrease the number of blood cells produced by the body.</p>
<p>Fit (seizures/convulsions)</p>	<p>Clozapine may cause patients to experience uncontrolled movements and spasms, particularly at the beginning of treatment course.</p>	<p>Patients are advised not to take clozapine if they suffer from uncontrolled epilepsy and to tell their doctor if they suffer from or have ever suffered from controlled</p>

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>Uncontrolled movements may also be a symptom of clozapine overdose.</p>	<p>epilepsy (seizures or fits), as the dosage may need to be adjusted.</p> <p>Patients are advised to inform their doctor immediately or visit their nearest hospital casualty department, if they notice uncontrolled movements/spasms or muscle jerking. Furthermore, patients are urged to contact their physician or call for emergency medical help immediately if they believe to have taken too many tablets or if anyone else has taken any of their tablets.</p>
<p>Heart attack and other events related to the heart and blood vessels  (Cardiovascular events - myocarditis, cardiomyopathy, myocardial infarction, orthostatic hypotension)</p>	<p>Several heart problems and blood vessels related events can occur during clozapine treatment, namely postural hypotension (form of low blood pressure that happens when you stand up from sitting or lying down), myocarditis (inflammation of the heart), pericarditis (heart inflammation and swelling of the tissue covering the heart)/</p>	<p>Patients are advised not to take clozapine if they suffer from any severe heart disease or if ever had to stop taking clozapine due to serious side effects such as heart problems. Patients are recommended to inform their physicians in case they are at risk for having a stroke, for example if they have high blood pressure,</p>

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>pericardial effusion (abnormal amount of fluid between the heart and the pericardium, which is the sac surrounding the heart), heart attack and cardiomyopathy (disease of the heart muscle that affect the size and shape of your heart and can also affect the way the electrical system makes your heart beat).</p>	<p>heart problems or blood vessel problems in the brain.</p> <p>Patients are urged to immediately contact their doctor in case they experience fast and irregular heartbeat, even at rest, palpitations, breathing problems, chest pain or unexplained tiredness. Their physician will need to check their heart and if necessary they might be immediately referred to a cardiologist.</p> <p>In addition patients are advised to be cautious when getting up from a sitting or lying position if clozapine makes them feel light-headed, dizzy or faint.</p>
<p>Obstruction of a blood vessel by a blood clot</p> <p>Blood clot, usually in a leg, which causes pain swelling or redness</p> <p>(Thromboembolism)</p>	<p>Cases of obstruction of a blood vessel by a blood clot that has become dislodged from another site in the circulation</p> <p>(thromboembolism) and cases of formation of blood clots in a vein (venous</p>	<p>Before starting treatment with clozapine patients are advised to inform their physician in case they suffer from or have ever suffered from blood clots or have a family history of blood clots, as medicines like</p>

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>thromboembolism) have been reported with the use of clozapine.</p>	<p>these have been associated with formation of blood clots.</p> <p>Patients are recommended to discuss with their physician the fact that they are taking clozapine if they have to undergo surgery or if for some reason they are unable to walk around for a long time, as they may be at risk of blood clotting within a vein.</p> <p>Patients should inform their physicians in case they are taking warfarin (medicine used to prevent blood clots).</p>
<p>Alteration in blood lipids, elevated blood sugar levels and weight gain  (Metabolic changes - weight gain, diabetes mellitus, dyslipidemia)</p>	<p>Clozapine, like other similar drugs, has been associated with weight gain, elevated blood sugar levels (diabetes) and alteration in blood lipids, which may increase the risk of stroke/heart related events.</p>	<p>Before starting treatment with clozapine patients are advised to inform their physician if they suffer from or have ever suffered from diabetes or if anyone in their family has suffered from diabetes. If patients suffer from high levels of sugar in the blood their doctor may regularly check their level of sugar in the blood.</p>

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
		<p>Patients are urged to contact their physician or if serious visit the nearest hospital casualty department, if they notice extreme thirst whilst passing large volumes of urine, feel tired or very hungry. These may be signs of diabetes, a condition where the level of glucose in the blood is raised. If left untreated, this can very rarely lead to coma or ketoacidosis.</p>
<p>Abnormal conduction in the heart causing irregular heartbeat  (QT-prolongation)</p>	<p>Very rare events of QT-prolongation have been observed with the use of clozapine, although there is no conclusive causal relationship to the use of this medicine. As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase the QTc interval.</p>	<p>Patients are advised to inform their physician in case they have had a heart disease or have family history of an abnormal conduction in the heart called “prolongation of the QT interval”.</p>

**Important potential risks**

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known (Including reason why it is considered a potential risk)</b>
<p>Stroke in elderly patients with dementia (Cerebrovascular events in elderly with dementia)</p>	<p>An increased risk of stroke has been seen with some atypical antipsychotics in clinical trials in population suffering from dementia. Clozapine should be used with caution in patients with risk factors for stroke.</p> <p>In elderly people with dementia, a small increase in the number of people dying has been reported for patients taking antipsychotics compared with those not taking antipsychotics. Clozapine is not approved for the treatment of dementia-related behavioural disturbances.</p> <p>Patients are recommended to inform their physician or pharmacist if they suffer from a condition called dementia.</p>
<p>Sudden death (Sudden death)</p>	<p>Sudden, unexplained deaths are known to occur both among treated (conventional antipsychotic medication) and untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving clozapine.</p> <p>The risk of sudden, unexplained death is adequately addressed to patients.</p>
<p>Kidney failure (Renal failure)</p>	<p>Clozapine is contraindicated in patients which suffer from severe kidney disorders. Renal and urinary disorders have been reported in association with clozapine therapy.</p> <p>Patients are advised against taking clozapine in case they suffer from any severe kidney disease. Before starting treatment with clozapine patients are recommended to inform they physician in case they suffer from or have ever suffered from any kidney disease.</p>

**Risk Management Plan [Clozapine] Version 2.0**

<b>Risk</b>	<b>What is known (Including reason why it is considered a potential risk)</b>
<p>Withdrawal reactions (rebound withdrawal effects)</p>	<p>Acute withdrawal reactions have been reported following abrupt stoppage of clozapine therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary, the patient should be carefully monitored for the following symptoms: 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.</p> <p>New-born babies of mothers that have used clozapine in the last trimester (last three months of their pregnancy) may suffer from the following symptoms: shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. Patients are advised to contact their physician in case their baby develops any of the above mentioned symptoms.</p>

**Missing information**

<b>Risk</b>	<b>What is known</b>
<p>Use in pregnant and breast-feeding patients (Use in pregnant and lactating patients)</p>	<p><u>Pregnant women</u></p> <p>There is only limited data on pregnant women with clozapine. If patients who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, are advised to refer to their physician or pharmacist for advice before taking clozapine. Physicians will discuss with them the benefits and possible risks of using this medicine during pregnancy. Patients are urged to immediately inform their physician if they become pregnant during treatment with clozapine.</p>

## Risk Management Plan [Clozapine] Version 2.0

Risk	What is known
	<p>The following symptoms may occur in new-born 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. Patients are advised to contact their physician in case their baby develops any of the above mentioned symptoms.</p> <p><u>Breast-feeding women</u></p> <p>Animal studies suggest that clozapine passes into breast milk and has an effect in the nursing infant. Patients are advised against breast-feeding during treatment with clozapine.</p>
Use in children and adolescents  (Use in children and adolescents)	<p><u>No paediatric studies have been performed and there is not enough information on clozapine's use in children and adolescents. Patients under 16 years of age you should not use clozapine.</u></p>

### VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development plan

No post-authorisation development has been planned as this is a generic drug application.

**Risk Management Plan [Clozapine] Version 2.0**

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

<b>Version</b>	<b>Date</b>	<b>Safety Concerns</b>	<b>Comment</b>
Version 2.0	25-Feb-2016	<p>The following safety concerns were added in the sequence depicted below.</p> <p>Important identified risks: agranulocytosis, seizures/convulsions, cardiovascular events (myocarditis, cardiomyopathy, myocardial infarction, orthostatic hypotension), neuroleptic malignant syndrome, thromboembolism, metabolic changes (weight gain, diabetes mellitus, dyslipidemia), QT-prolongation;</p> <p>Important potential risks: cerebrovascular events in elderly with dementia, sudden death, renal failure and rebound withdrawal effects;</p> <p>Missing information: use</p>	<p>This RMP was updated from version 1.0 to version 2.0 in line with RMS Day 70 Preliminary Assessment Report for Clozapin Vale (clozapine), procedure number SE/H/1496/01-02/DC, dated 16-Nov-2015.</p>

**Risk Management Plan [Clozapine] Version 2.0**

<b>Version</b>	<b>Date</b>	<b>Safety Concerns</b>	<b>Comment</b>
		in pregnant and lactating patients and use in children and adolescents.	