
PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

LEVOMEPRMAZINE ORION

5 MG, 25 MG, 50 MG AND 100 MG TABLET

(LEVOMEPRMAZINE MALEATE)

ORION CORPORATION

DATE: 28-03-2017, VERSION 1.1

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Levomepromazine Orion is indicated for the treatment of schizophrenia and other psychoses and for severe pain, either alone or in combination with appropriate analgesics.

Schizophrenia is a mental disorder in which people interpret reality abnormally. Schizophrenia tends to first develop (or at least become evident) between adolescence and young adulthood, typically between the ages of 16 - 30 years. Men are more likely than women to develop it at an earlier age and to experience more severe symptoms. The causes of schizophrenia are not yet fully understood. It may develop from a combination of genetic, brain chemistry, and environmental factors. Schizophrenia's symptoms are typically described as "positive" or "negative." Positive symptoms include delusions (false beliefs), thought disorders, and hallucinations (person may hear voices other people don't hear, or believe other people are reading their minds, controlling their thoughts, or plotting to harm them). Negative symptoms include avolition (a lack of desire or motivation to accomplish goals), lack of desire to form social relationships, and blunted emotion. The treatment for schizophrenia generally includes a combination of medication, inpatient treatment, residential or day treatment therapy, and vocational training.

Pain is the most common symptom of injury and disease, and descriptions can range in intensity from a mere ache to unbearable agony (severe). Pain arises from any number of situations. There are many drugs aimed at preventing or treating pain. These may include: nonopioid, narcotic, anticonvulsant drugs, and tricyclic antidepressants. Drugs from different classes may be combined to handle certain types of pain.

VI.2.2 Summary of treatment benefits

The active substance of Levomepromazine Orion, levomepromazine, is an antipsychotic, used mainly for the treatment of severe mental disorders (schizophrenia, psychoses). It prevents certain substances in the brain to work, and therefore alleviates symptoms of psychosis. In addition, it can also be used for the treatment of severe pain either alone or in combination with other pain killers.

VI.2.3 Unknowns relating to treatment benefits

Safety in pregnancy and during lactation has not been established. There are no or limited amount of data from the use of levomepromazine in pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Disruption in the functioning of fatty, vascular tissue that fills most of the bones and is involved in the formation of blood cells (Bone marrow function disorders including agranulocytosis)	Levomepromazine may cause a reduction in the number of white blood cells (blood cells that help in fighting infections). Also agranulocytosis (severe reduction in the number of certain white blood cells) has been observed during treatment with levomepromazine. Reduction of white blood cells may lead to decreased resistance to infections.	If the person experience an infection with symptoms such as fever and serious deterioration of general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems, one should see the doctor immediately. It is advisable to determine blood count before and during levomepromazine therapy regularly.
Disruption in the functioning of heart (Cardiac disorders)	Levomepromazine may cause prolongation of QT interval (abnormality in the heart's	Levomepromazine should be used with caution in patients with decreased heart rate and

Risk	What is known	Preventability
	<p>electrical system) in a dose dependent manner.</p> <p>Cases of Torsades de Pointes (life threatening, abnormal heart rhythms) and sudden deaths have been reported.</p> <p>Levomepromazine may cause drop in blood pressure (hypotension). This usually occur at the beginning of the treatment and disappear with continued treatment.</p> <p>Electrolyte disturbances like low potassium and magnesium levels increase the risk of severe/life-threatening arrhythmias (abnormal heart rhythms).</p>	<p>those having a family history of long QT interval. In addition, coadministration with other medicines causing QT interval prolongation should be avoided.</p> <p>Physician should be informed if the patient uses other medicines concomitantly.</p> <p>The hypotensive effect of levomepromazine should be taken into consideration when administered to weak patients, elderly patients or patients with heart failure or some other cardiac disease. Patients receiving large doses should be kept in bed.</p> <p>Electrolyte disturbances should be corrected before initiating therapy and also during the therapy.</p>
<p>Abnormal involuntary movements, alterations in muscle tone, and postural disturbances (Extrapyramidal adverse reactions and other neurological disorders)</p>	<p>Levomepromazine may cause tardive dyskinesia whose symptoms are rhythmical, involuntary movements of the tongue, face, mouth or jaws, sometimes associated with involuntary movements of the limbs.</p> <p>Levomepromazine may also cause neuroleptic malignant syndrome, whose symptoms are fever, excessive sweating, muscle rigidity, altered mental state, heart rhythm disturbances or wide fluctuations in one's blood pressure. This syndrome is, if not treated, life-threatening and in worst cases may result in death.</p>	<p>Physician should be contacted immediately if any signs indicative of neuroleptic malignant syndrome or tardive dyskinesia appear.</p> <p>Given the potential for extrapyramidal side-effects and tardive dyskinesia, levomepromazine is not recommended under the age of 18 years.</p>
<p>A blood clot that forms in a vein and migrates to another location (Venous thromboembolism)</p>	<p>Cases of venous thromboembolism including cases of deep vein thrombosis (condition in which blood clots form inside the veins resulting in obstruction of venous flow) and cases of pulmonary embolism (life threatening condition when</p>	<p>Physician should be informed if patient or his/her family has history of blood clots.</p>

Risk	What is known	Preventability
	a blood clot travels to lungs leading to problems with respiration/breathing) have been reported with antipsychotic drugs.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Death in elderly patients with dementia	In elderly people with dementia (a chronic/persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning), a small increase in the number of deaths has been reported for patients taking antipsychotics compared with those not receiving antipsychotics.

Missing information

Risk	What is known
Use in pregnant and lactating women	Safety in pregnancy has not been established. There are no or limited amount of data from the use of levomepromazine in pregnant women. Levomepromazine crosses the placenta. Levomepromazine should not be used during the first trimester of pregnancy and a treatment at the lowest effective dose should be considered in the second and third trimester only, if clearly necessary weighing the benefit to the mother against the risk to the child. Neonates exposed to antipsychotics (including Levomepromazine Orion) 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. Consequently, newborns should be monitored carefully. Safety during breastfeeding has not been established. Levomepromazine is excreted in breast milk. Women who are breastfeeding should therefore be advised to avoid breast-feeding while taking levomepromazine.
Use in elderly	Doses that are prescribed to elderly patients are usually lower compared to other adults. This is because elderly patients are more sensible for side effects.
Use in children	Levomepromazine use is not recommended for children and adolescents under the age of 18 years due to concerns regarding possible side effects.
Use in severe kidney disease (Use in severe renal insufficiency)	Physician should be informed if patient suffers from kidney disease. Considerable caution should be exercised and the lowest effective dose should be aimed.
Use in severe liver disease (Use in severe hepatic insufficiency)	Physician should be informed if patient suffers from liver disease. Considerable caution should be exercised and the lowest effective dose should be aimed.

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. The Summary of Product Characteristics and the Package leaflet for Levomepromazine Orion can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.

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Date dd.mm.yyyy (UTC)	Justification	Electronically signed by
12.07.2017 12:40:18	Reviewed	Miettinen Antti (antmie)