VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Multiple myeloma

Multiple myeloma (MM) is a debilitating malignancy that is part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukaemia.

The proliferation of plasma cells in MM may interfere with the normal production of blood cells, resulting in leukopenia, anaemia, and thrombocytopenia. The cells may cause soft-tissue masses (plasmacytomas) or lytic lesions in the skeleton. Feared complications of MM are bone pain, hypercalcemia, renal failure, and spinal cord compression.

MM accounts for 10% of all hematologic cancers. The age-adjusted annual incidence of MM is 4.3 cases per 100,000 white men, 3 cases per 100,000 white women, 9.6 cases per 100,000 black men, and 6.7 cases per 100,000 black women.

The 5-year relative survival rate for MM is 46.6%. Survival is higher in younger people and lower in the elderly.

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, lenalidomide represents an effective drug in the treatment multiple myeloma.

If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions, lenalidomide can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Harmful effects to an unborn child *(Teratogenicity)*	Lenalidomide is expected to be harmful to an unborn child.	<u>For women taking lenalidomide</u> Effective methods of contraception must be used if you are a woman of childbearing potential. If pregnancy occurs during treatment with lanelidomide, the treatment should be stopped and the doctor should be informed immediately. If able to become pregnant pregnancy tests will be performed under the supervision of the doctor (before every treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished) except where it has been confirmed that the fallopian tubes have been severed and sealed, to stop eggs from reaching the uterus (tubal sterilisation). <u>For men taking lenalidomide</u> If the partner becomes pregnant whilst taking lenalidomide, the doctor should be informed immediately. It is recommended that the partner seeks medical advice. Effective methods of contraception must be used.
Reduction in blood platelets, which increases risk of bleeding *(Thrombocytopenia and bleeding)*	Lenalidomide may reduce the number of the blood cells which help the blood to clot (platelets) which may lead to bleeding disorders such as nosebleeds and bruising.	A blood test should be done: - before treatment - every week for the first 8 weeks of treatment - then at least every month after that.

Risk	What is known	Preventability
Low blood cells that help fight infection *(Neutropenia) and infection*	Lenalidomide may reduce the number of white blood cells that fight infection.	A blood test should be done: - before treatment - every week for the first 8 weeks of treatment - then at least every month after that.
Blood clot *(Thromboembolic events)*	Lenalidomide may also cause blood clots in the veins (thrombosis).	The doctor should be informed if you experience: - leg pain (which could be a symptom of thrombosis), - chest pain or shortness of breath (which may be a symptom of blood clots in the lungs, called pulmonary embolism).
Skin reaction *(Cutaneous reactions)*	Lenalidomide may cause redness of skin, rashes, tingling or burning sensation to the skin, dry skin, darkening of the skin, skin eruptions, skin cracking, flaking or peeling skin, changes to the colour of your skin, sensitivity to sunlight and serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body (Stevens-Johnson syndrome and/or toxic epidermal necrolysis).	The doctor, pharmacist or nurse should be consulted if any side effects occur.
Serious allergic reaction which causes swelling of the face or throat *(Hypersensitivity and angioedema)*	Lenalidomide should not be used if allergic to lenalidomide or any of the other ingredients of the medicine.	The doctor should know if the patient has had an allergic reaction whilst taking thalidomide (another medicine used to treat multiple myeloma) such as rash, itching, swelling, dizziness or trouble breathing.
Diarrhoea and constipation	Diarrhoea and constipation are very common side effects of lenalidomide treatment.	The doctor, pharmacist or nurse should be consulted if any side effects occur.
Dying cancer cells disintegration *(Tumour lysis syndrome (TLS))*	Tumour lysis syndrome - metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the break-down products of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heart beats, seizures, and sometimes death.	The doctor, pharmacist or nurse should be consulted if any side effects occur.

Risk	What is known	Preventability
Cancer of blood-forming cells in the bone marrow in patients newly diagnosed with multiple myeloma *(Acute myeloid leukaemia (AML and B-cell malignancies for newly diagnosed multiple myeloma (NDMM))*	It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with lenalidomide treatment.	The doctor should carefully evaluate the benefit and risk when prescribing lenalidomide.
Skin cancer other than melanoma in patients returning multiple myeloma *(Non melanoma skin cancer (NMSC) for relapsed and/or refractory multiple myeloma (RRMM))*	It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with lenalidomide treatment.	The doctor should carefully evaluate the benefit and risk when prescribing lenalidomide.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
A disorder of the nerves which can cause weakness, tingling or numbness *(Peripheral neuropathy)*	Limited information is available on peripheral neuropathy.
Heart problems which can cause shortness of breath or ankle swelling *(Cardiac failure)*	Lenalidomide may cause shortness of breath especially when lying down (which may be a symptoms of heart failure).
Irregular heart beat *(Cardiac arrhythmias)*	Lenalidomide may cause slow, fast or irregular heart beat.
Kidney failure *(Renal failure)*	Lenalidomide may cause kidney problems, passing much more or much less urine than usual, which may be a symptom of a type of kidney problem (called renal tubular necrosis).

Risk	What is known (Including reason why it is considered a potential risk)
Heart attack *(Ischaemic heart disease (including myocardial infarction))*	Lenalidomide may cause chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting, which may be symptoms of a heart attack (myocardial infarction).
Inflammation of the lungs which causes breathlessness, cough and raised temperature *(Interstitial lung disease (interstitial pneumonitis))*	Lenalidomide may cause wheezing, shortness of breath or a dry cough, which may be symptoms caused by inflammation of the tissue in the lungs.
Liver disorders *(Hepatic disorders)*	Lenalidomide may cause abnormal liver test results, yellow pigmentation to the skin, mucus membrane or eyes (jaundice), pale coloured stools, dark coloured urine, skin itch, rash, pain or swelling of the stomach –these may be symptoms of injury to the liver (hepatic disorder).
Off-label use	The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system.
Skin cancer other than melanoma in patients newly diagnosed with multiple myeloma *(NMSC for NDMM)*	It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with lenalidomide treatment.
Cancer of blood-forming cells in the bone marrow in patients returning multiple myeloma *(AML and B-cell malignancies for RRMM)*	It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with lenalidomide treatment.
Other second primary malignancies (SPM) (ie, those not detailed above for the NDMM and RRMM populations)	It is important to note that a small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with lenalidomide treatment.

Missing information

Risk	What is known
Use in paediatric population *(Paediatric use)*	Lenalidomide is not recommended for use in children and adolescents under 18 years.
Use in patients with liver disorders *(Use in moderate and severe hepatic impairment)*	Limited information is available on use in moderate and severe hepatic impairment.
Use in breastfeeding	Female patients must not breast-feed when taking lenalidomide, as it is not known if lenalidomide passes into human milk.

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 Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

In addition, this medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Harmful effects to an unborn child *(Teratogenicity)* and off-label use

Risk minimisation measures: • **The Educational Healthcare Professional's Kit** • **Educational Brochures for patients** • **Patient Card**
Objective and rationale: Patients and HCPs to understand the risk of harmful effects to an unborn child *(teratogenicity)* and the appropriate management of this risk to minimise its occurrence and its severity.
Summary description of main additional risk minimisation measures – Description of the PPP and categorisation of patients based on sex and childbearing potential – Safety advice for women of childbearing potential – Safety advice for men – Requirements in the event of pregnancy – Verification that appropriate counselling has taken place – Documentation of childbearing status potential – Pregnancy test dates and results

Risk minimisation measures: • **The Educational Healthcare Professional's Kit** • **Educational Brochures for patients** • **Patient Card**
Proposed action: • The Educational Healthcare Professional's Kit to be provided to prescribing physicians • Educational Brochures for patients will inform patients that lenalidomide has expected harmful effects to an unborn child and the importance of informing their HCP if any occur • Patient card to verificate that appropriate counselling has taken place, documente of childbearing status potential and pregnancy test dates and results

Reduction in blood platelets, which increases risk of bleeding *(Thrombocytopenia and bleeding)*

Risk minimisation measures: • **The Educational Healthcare Professional's Kit** • **Educational Brochures for patients**
Objective and rationale: Patients and HCPs to understand the risk of reduction in blood platelets, which increases risk of bleeding (thrombocytopenia and bleeding) and the appropriate management of this risk to minimise its occurrence and its severity.
Summary description of main additional risk minimisation measures – Description and management of thrombocytopenia
Proposed action: • The Educational Healthcare Professional's Kit to be provided to prescribing physicians • Educational Brochures for patients will inform patients that lenalidomide may cause thrombocytopenia and the need for regular blood tests

Low blood cells that help fight infection *(Neutropenia) and infection*

Risk minimisation measures: • **The Educational Healthcare Professional's Kit** • **Educational Brochures for patients**
Objective and rationale: Patients and HCPs to understand the risk of low blood cells that help fight infection (neutropenia) and infection and the appropriate management of this risk to minimise its occurrence and its severity.
Summary description of main additional risk minimisation measures – Description and management of neutropenia
Proposed action: • The Educational Healthcare Professional's Kit to be provided to prescribing physicians • Educational Brochures for patients will inform patients that lenalidomide may cause neutropenia and the need for regular blood tests

Blood clot *(Thromboembolic events)*

Risk minimisation measures: • **The Educational Healthcare Professional's Kit**
Objective and rationale: HCPs to understand the risk of blood clot (thromboembolic events) and the appropriate management of this risk to minimise its occurrence and its severity and to give safety advice regarding this risk to all patients.
Summary description of main additional risk minimisation measures – Description and management of thromboembolic risk
Proposed action: • The Educational Healthcare Professional's Kit to be provided to prescribing physicians

A disorder of the nerves which can cause weakness, tingling or numbness *(Peripheral neuropathy)*

Risk minimisation measures: • **The Educational Healthcare Professional's Kit**
Objective and rationale: HCPs to understand the risk of a disorder of the nerves which can cause weakness, tingling or numbness (peripheral neuropathy) and the appropriate management of this risk to minimise its occurrence and its severity and to give safety advice regarding this risk to all patients.
Summary description of main additional risk minimisation measures – Explanation of unknown risk of neuropathy with long term use
Proposed action: • The Educational Healthcare Professional's Kit to be provided to prescribing physicians

Use in patients with liver disorders (Use in moderate and severe hepatic impairment)

Risk minimisation measures: • **The Educational Healthcare Professional's Kit**
Objective and rationale: HCPs to understand the risk of use in patients with liver disorders (use in moderate and severe hepatic impairment) and the appropriate management of this risk to minimise its occurrence and its severity.
Summary description of main additional risk minimisation measures – Give safety advice to all patients
Proposed action: • The Educational Healthcare Professional's Kit to be provided to prescribing physicians

VI.2.6 Planned post-authorisation development plan

Not applicable.

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

Not applicable for pre-approval versions.