VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Multiple myeloma (MM) is a cancer of the blood, affecting mostly elderly people, men more than women. It is the second most common blood cancer in the European Union (EU), accounting for approximately 13% of blood cancers and 1% of tumors. The yearly rate of new cases of MM is about 3 per 100,000 persons in the EU. MM affects plasma cells, a type of white blood cell that normally produces proteins to fight infections. MM may progress, leading to organ damage.

The cause of MM is unknown but starts with an abnormal plasma cell growing in the bone marrow more than it should and affects production of healthy cells.

Risk factors for MM include increasing age, sex (male), race (twice as common among blacks vs whites), radiation exposure, family history, and workplace exposures.

VI.2.2 Summary of Treatment Benefits

Ixazomib, together with lenalidomide and dexamethasone, is used for adult patients with MM who have received at least 1 prior therapy.

Ixazomib has been studied in combination with 2 drugs commonly used to treat MM (lenalidomide and dexamethasone, referred to as LenDex). This combination was compared to placebo (a non-drug pill) and LenDex for the treatment of MM. Although multiple treatments are available for MM, the relapses that characterize this disease highlight a need for new therapies for patients whose prior treatments have failed and their disease has returned. The benefits were shown in a large, global, randomized double-blind placebo-controlled trial where patients treated with the ixazomib regimen lived longer without their disease worsening. The regimen was well tolerated overall, and side effects were manageable.

VI.2.3 Unknowns Relating to Treatment Benefits

In the phase 3 study of ixazomib with LenDex, patients lived longer without their disease worsening regardless of age, sex, or race. Studying side effects and product usage over time will determine the benefits and risks of long-term treatment.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Low platelet count (Thrombocytopenia)	Platelets are cells in your blood that are necessary to form clots and stop bleeding. A low number of platelets might impair your body's ability to adequately form clots. In the ixazomib clinical studies, low platelet counts were seen with ixazomib in combination with LenDex. The low platelets did not result in an increase of hemorrhage (bleeding) or platelet transfusions.	As part of your routine care, your doctor should monitor your platelet counts frequently. The dose of ixazomib can be adjusted by your doctor.
Severe gastrointestinal (GI) events (specifically nausea, vomiting, diarrhea)	The class of drugs used to treat MM have been known to cause events that affect the stomach and bowel movements. In the clinical studies with ixazomib, events such as nausea, vomiting, and diarrhea were reported more often in patients who received ixazomib in combination with LenDex; however, few potential complications (eg, weight loss or dehydration) were reported. Nausea, vomiting, and diarrhea reported in the ixazomib clinical development program were frequently mild or moderate in severity and manageable by standard clinical measures or dose modifications.	Your doctor can check your weight, nutrition status, and fluid intake. Nausea, vomiting, and diarrhea should be monitored in patients treated with ixazomib. Routine medical care such as intravenous (IV) fluids or electrolyte replacement can be used to treat severe symptoms, as determined by your doctor. Your doctor may prescribe medications used to prevent or treat diarrhea, nausea, and vomiting. Gastrointestinal (GI) symptoms like nausea, vomiting, and diarrhea, may cause discomfort and potentially limit your activities, nutrition, and social activities.
Numbness, tingling, pain, or burning of the hands or feet (Peripheral neuropathy)	Feelings of numbness, tingling, pain, or burning of the hands and feet, or peripheral neuropathy, have been known to occur with ixazomib and other drugs used to treat MM.	Your doctor should monitor for symptoms of neuropathy. If you experience new or worsening symptoms such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs, the dose of ixazomib can be adjusted by your doctor.

Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
Severe skin rashes (Severe dermal events)	Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores (eg, Stevens-Johnson Syndrome) have been reported though the cause is not clear. These skin conditions are disorders of the immune system, which differ from regular skin rashes and are generally more severe.
Shingles (Herpes zoster infections)	Patients that are immunosuppressed may be at an increased risk of reactivation of the chicken pox virus (shingles) that can cause a skin rash and local pain (herpes zoster). Herpes zoster infections have been reported.
Condition of the nervous system that can cause changes in vision, changes in mental status, or seizures (Posterior reversible encephalopathy syndrome)	Posterior reversible encephalopathy syndrome is a condition which affects the brain and is characterized by headache, seizures, and visual loss, as well as an abrupt increase in blood pressure. It often gets better by stopping treatment.

Missing Information

Risk	What is Known
Use in pregnancy / lactation	Patients who were pregnant or breast-feeding were not allowed to participate in ixazomib clinical trials. NINLARO will be used in combination with lenalidomide, a known teratogen (harmful to unborn baby); therefore, particular attention to pregnancy testing and prevention as required by the lenalidomide label and Pregnancy Prevention Programme should be adhered to. NINLARO is not recommended during pregnancy as it may harm your unborn baby. Breast-feeding should be stopped when taking NINLARO. Avoid becoming pregnant or breastfeeding while being treated with NINLARO. If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you are a woman of childbearing potential or a man who can father a child, you must use effective contraception during and for 90 days after treatment. Women using hormonal contraceptives should additionally use a barrier method of contraception. Tell doctor right away if you or your partner become pregnant while receiving NINLARO.
Long-term safety	There was limited long-term use of ixazomib in the primary clinical study.

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

Not applicable. There are no additional risk minimization measures for ixazomib.

VI.2.6 Planned Postauthorization Development Plan

List of Studies in Post-authorization Development Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
C16010 [Category 1]* A phase 3, randomized, double-blind study C16010 in adult patients with relapsed and/or refractory multiple myeloma	The safety objective is to determine the safety of the addition of ixazomib to lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with RRMM.	Long-term safety	Ongoing As of 01 June 2015, 722 patients have been randomized in the study.	December 2019
C16019 [Category 2]** A phase 3, randomized, placebo-controlled, double-blind study ixazomib in maintenance therapy in patients with multiple myeloma following SCT	The safety objective is to determine the long-term safety and tolerability of ixazomib administration to patients with MM following ASCT.	Long-term safety	Ongoing As of 01 June 2015, 236 patients have been randomized in the study.	December 2018

Abbreviations ASCT=autologous stem cell transplantation, MM=multiple myeloma, PFS=progression-free survival, RRMM=relapsed and/or refractory multiple myeloma.
*C16010 is listed as a Category 1 study in Part III (PhV Plan) as it is also a Post-authorisation efficacy study (PAES) listed in Part IV (Efficacy development plan) with Imposed obligation.
** C16010 is listed as a Category 2 study in Part III (PhV Plan) as it is also a Post-authorisation efficacy study (PAES) listed in Part IV (Efficacy development plan) with Specific obligations.

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports
Post-authorisation efficacy study (PAES) C16010 [Category 1]: A phase 3, randomized, double-blind study C16010 in adult patients with relapsed and/or refractory multiple myeloma	To continue to follow for overall survival	Efficacy (OS) in patients with relapsed and/or refractory multiple myeloma	Started	December 2019
C16010 China Continuation Study: [Category 2] A phase 3, randomized, double-blind, multicenter study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide in patients with relapsed and/or refractory multiple myeloma	To continue to follow for overall survival	Efficacy (OS) in patients with relapsed and/or refractory multiple myeloma	Started	December 2016
C16014: [Category 2] A phase 3, randomized, double-blind, multicenter study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma not eligible for SCT	To demonstrate improvement in PFS in non-transplant eligible newly diagnosed multiple myeloma patients	Efficacy (PFS) in patients with newly diagnosed multiple myeloma not eligible for SCT	Started	December 2017
C16019: [Category 2] A phase 3, randomized, placebo-controlled, double-blind study ixazomib in maintenance therapy in patients with multiple myeloma following SCT	To demonstrate improvement in PFS after stem cell transplant in newly diagnosed multiple myeloma patients	Efficacy (PFS) in patients with newly diagnosed multiple myeloma after SCT	Started	December 2018

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports
NSMM-55001 [Category 2]: A global, prospective, non-interventional, observational study of multiple myeloma patients	To provide real life descriptive data on patterns of treatment and outcomes	Descriptive data on 1000 patients including 200 RRMM patients treated with ixazomib	Started	December 2019

Abbreviations: OS=overall survival, PFS=progression-free survival, RRMM=relapsed and/or refractory multiple myeloma, SCT=stem cell transplantation.

Studies That Are a Condition of the Marketing Authorization

Study C16010 is a condition of the marketing authorization.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Not applicable.