PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Evenity®

This is a summary of the risk management plan (RMP) for Evenity. The RMP details important risks of Evenity, how these risks can be minimized, and how more information will be obtained about Evenity's risks and uncertainties (missing information).

Evenity's summary of product characteristics (SmPC) and its patient information leaflet (PIL) give essential information to healthcare professionals and patients on how Evenity should be used.

This summary of the RMP for Evenity should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Evenity's RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Evenity is authorised for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture (see SmPC for the full indication). It contains romosozumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Evenity's benefits can be found in Evenity's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/evenity.

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

Important risks of Evenity, together with measures to minimize such risks and the proposed studies for learning more about Evenity's risks, are outlined below.

Measures to minimize the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Evenity, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Evenity is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing information

Important risks of Evenity are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Evenity. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 2–1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hypersensitivity Immunogenicity (development of antibodies to romosozumab) Hypocalcemia Serious cardiovascular events of myocardial infarction and stroke
Important potential risks	Osteonecrosis of the jaw Atypical femoral fracture Serious infections Cardiac arrhythmias
Missing information	Osteoporosis rebound effects

2.2 Summary of important risks

Table 2–2: Summary of important risks

Important identified risk: hypersensitivity	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Known hypersensitivity to romosozumab and any of its excipients.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration).

Table 2–2: Summary of important risks

	SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use) and SmPC Section 4.8 (Undesirable effects). Further information is also provided in the PIL. Additional risk minimization measures: None
Important identified risk: immunogenicity (development of antibodies to romosozumab)	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	No risk groups or risk factors have been identified during the clinical studies.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.8 (Undesirable effects) Additional risk minimization measures: None
Important identified risk: hypocalcemia	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30mL/min), dialysis, and some medications.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.2 (Posology and method of administration), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.8 (Undesirable effects). Recommendations for prevention and monitoring of signs and symptoms of hypocalcemia are included in SmPC Section 4.4 and SmPC Section 4.2. No dose adjustment is required in patients with renal impairment (SmPC Section 4.2). Recommendation for monitoring of calcium levels in patients with severe renal impairment or receiving dialysis is included in SmPC Section 4.4. Further information is also provided in the PIL.

Table 2–2: Summary of important risks

	Additional risk minimization measures: Prescriber Guide and Patient Alert Card
Important identified risk: serious cardiovascular events of myocardial infarction and stroke	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies, and pharmacoepidemiological background prevalence rates. This risk has been detected based on an imbalance of myocardial infarction and stroke events between romosozumab and alendronate in 1 of the 2 pivotal fracture studies, the alendronate-controlled study, 20110142 in women. The imbalance resulted from small differences in terms of absolute subject numbers and absolute risk differences. No imbalance of cardiovascular events was observed in the larger placebo-controlled fracture study 20070337 in women. In study 20110174 in men, the differences in incidence of serious cardiac ischemic events and cerebrovascular events reported between the romosozumab group and placebo were less apparent; the absolute number of events was small. No evidence of any mechanistic association between sclerostin inhibition and atheroprogression or MACE-1 events was established based on the totality of nonclinical evidence including 2 recent studies evidence.
Risk factors and risk groups	The romozosumab osteoporosis development program was conducted in an older subject population who are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population. Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including anthracyclines, antipsychotic agents, nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors. Patients with a history of myocardial infarction or stroke have highest absolute risk of major adverse cardiac events.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PIL. Additional risk minimization measures: Prescriber Guide, Patient Alert Card and information letter
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - European non-interventional post-authorization safety study related to the adherence to the risk minimization measures (effectiveness on behavior) by the EU-ADR Alliance. - European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the EU-ADR Alliance.

Table 2–2: Summary of important risks

	See Section 2.3 of this summary for an overview of the post-authorization development plan.
Important potential risk: osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Risk factors include bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) Further information is also provided in the PIL. Additional risk minimization measures: Prescriber Guide and Patient Alert Card
Important potential risk: atypical femoral fracture	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies and pharmacoepidemiological background prevalence rates. This risk was detected in the clinical trial setting.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, and hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) Further information is also provided in the PIL. Additional risk minimization measures: None
Important potential risk: serious infections	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies prevalence rates. This risk was detected in the clinical trial setting.

Table 2–2: Summary of important risks

Risk factors and risk groups	The romozosumab osteoporosis development program was conducted in an older subject population who is more affected by serious infections and with more severe consequences than the general population. Such infections typically include pneumonia, influenza, tuberculosis, bacteremia, nosocomial infection, urinary tract infection, salmonellosis and hepatitis. Risk factors for serious infections include impaired immune function, anatomic and functional changes such as pulmonary hypoventilation, bronchopulmonary aspiration, immobility and urinary retention, comorbidities such as diabetes and malignancy and institutionalization (in hospitals, or nursing homes).
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: European non-interventional post-authorization safety study related to serious infections for romosozumab by the EU-ADR Alliance. See Section 2.3 of this summary for an overview of the post-authorization development plan.
Important potential risk: cardiac arrhythmias	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derived from clinical studies and postmarketing cases. This risk was detected in the postmarketing setting (review of case reports within Eudravigilance and signal detection based on disproportionality) There is insufficient evidence to date to establish a causal relationship between the occurrence of cardiac arrhythmia and the use of romosozumab. However, while cofounding factors were reported in most of the cases which precluded an assessment of a causal relationship, some events were reported with a close temporal relationship. Furthermore; while an imbalance of MACE was observed within the pivotal Phase III study (Study 20110142), the precise etiology has yet to be elucidated and may be related to cardiac arrhythmia. Thus, the risk of cardiac arrhythmia will be considered as an important potential risk.
Risk factors and risk groups	An analysis of real-world data in the USA, as per the first interim report of the FDA postmarketing requirement, revealed that a greater proportion of women with PMO exposed to romosozumab compared to other osteoporosis medications were older had important comorbidities (eg, COPD, diabetes, hyperlipidemia, hypertension, and smoking habits) and pre-existing arrhythmia. These constitute strong predisposing risk factors for the risk of cardiac arrhythmia among romosozumab users.
Risk minimization measures	Routine risk minimization measures: Recommendations for evaluation of the individual benefit-risk balance is included in SmPC Section 4.4- (Special warnings and precautions for use). Additional risk minimization measures: None

Table 2–2: Summary of important risks

Additional pharmacovigilance activities	Additional pharmacovigilance activities: European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the EU-ADR Alliance. See Section 2.3 of this summary for an overview of the post-authorization development plan.
Missing information: Osteoporosis rebound effects	
Risk minimization measures	Routine risk minimization measures: Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis - SmPC Section 4.2 (Posology and method of administration). Recommendation of follow-on therapy in SmPC Section 4.2 (Posology). Additional risk minimization measures: None

PIL=Patient Information Leaflet; SmPC=Summary of Product Characteristics

2.3 Post-authorization development plan

2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are a condition of the marketing authorization or which are a specific obligation.

2.3.2 Other studies in post-authorization development plan

Additional pharmacovigilance activities include the followings:

2.3.2.1 European non-interventional post-authorization safety study related to adherence to the risk minimization measures for romosozumab by the EU-ADR Alliance

Study short name and title:

European non-interventional post-authorization safety study related to adherence to the risk minimization measures for romosozumab by the EU-ADR Alliance.

Purpose of the study:

Adherence to the risk minimization measures in the product information is planned to be studied by estimating the compliance with contraindications and target indication amongst incident romosozumab users and analyzing the utilization patterns.

2.3.2.2 European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke, and all-cause mortality for romosozumab by the EU-ADR Alliance

Study short name and title:

European non-interventional post-authorization safety study related to serious cardiovascular events of myocardial infarction and stroke and all-cause mortality for romosozumab by the EU-ADR Alliance.

Purpose of the study:

Serious cardiovascular events of myocardial infarction and stroke are considered an important identified risk and cardiac arrhythmias are considered an important potential risk for romosozumab.

The objective of the non-interventional post-authorization safety study is to characterize the serious cardiovascular events (myocardial infarction, stroke, all-cause, cardiovascular death and cardiac arrhythmias) in romosozumab users and in comparable patients receiving alternative osteoporosis medications. Events in scope were identified with previously validated algorithms by the EU-ADR Alliance members.

2.3.2.3 European non-interventional post-authorization safety study related to serious infections for romosozumab by the EU-ADR Alliance

Study short name and title:

European non-interventional post-authorization safety study related to serious infections for romosozumab by the EU-ADR Alliance.

Purpose of the study:

Serious infections are considered an important potential risk for romosozumab. To date no definitive determination of causality has been established.

The objective of the non-interventional post-authorization safety study is to characterize the serious infections in new romosozumab users and in comparable patients receiving alternative osteoporosis medications. Events in scope were specified using preparational validation studies to make sure the identification of the outcomes are accurate due to the absence of validated algorithms across the EU-ADR Alliance.