LABATEC PHARMA SA

Summary of the Risk Management Plan for Tymlos® (abaloparatide)

Version number: 0.5

Based on EU RMP version (please note that the brand name in the summary of the risk management plan is the one marketed in the EEA (Eladynos), while in Switzerland abalaparotide's brand name shall be Tymlos)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP Summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Tymlos® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Tymlos® in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Labatec Pharma SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tymlos®.

Part VI: Summary of the risk management plan

Summary of risk management plan for Eladynos 80 micrograms/dose solution for injection in pre-filled pen (abaloparatide).

This is a summary of the risk management plan (RMP) for Eladynos 80 micrograms/dose solution for injection in pre-filled pen. The RMP details important risks, how these risks can be minimised, and how more information will be obtained for risks and uncertainties (missing information).

Eladynos 80 micrograms/dose solution for injection in pre-filled pen's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Eladynos 80 micrograms/dose solution for injection in pre-filled pen should be used.

This summary of the RMP for Eladynos 80 micrograms/dose solution for injection in pre-filled pen 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 Eladynos 80 micrograms/dose solution for injection in pre-filled pen's RMP.

I. The medicine and what it is used for

Eladynos 80 micrograms/dose solution for injection in pre-filled pen is authorised for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. It contains abaloparatide as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Eladynos 80 micrograms/dose solution for injection in pre-filled pen's benefits can be found in Eladynos 80 micrograms/dose solution for injection in pre-filled pen'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/eladynos.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Eladynos 80 micrograms/dose solution for injection in pre-filled pen together with measures to minimise such risks and the proposed studies for learning more about Eladynos 80 micrograms/dose solution for injection in pre-filled pen's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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

II.A List of important risks and missing information

Important risks of Eladynos 80 micrograms/dose solution for injection in pre-filled pen are risks that need special risk management activities to further investigate or minimise 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 Eladynos 80 micrograms/dose solution for injection in pre-filled pen. 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 (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Osteosarcoma Serious cardiovascular events (i.e. MACE, arrhythmia)
Missing information	None

II.B Summary of important risks

Important identified risk:

None.

Important potential risk 1: Osteosarcoma	
Evidence for linking the risk to the medicine	In the general population, osteosarcoma is the most common nonhematological primary bone malignancy, however its incidence is rare (Cipriani, 2012). The incidence of osteosarcoma has a biphasic trend by age, with a first peak around puberty and a smaller peak in subjects over 60 years of age (Cipriani, 2012). The number of cases per million per year ranges worldwide between 3 and 4.5 in childhood and adolescence, 2 in individuals 25 to 59 years old, and 1.5 to 4.5 in subjects over the age of 60 years. The exaggerated anabolic response in rats indicates a significant anabolic stimulus driving osteoblast activity, likely stimulating a proliferative response (or preventing osteoblast apoptosis) (Jilka, 1999; Schnoke, 2009), and leading to an abnormal accumulation of osteoblasts, and osteosarcomas, in rodents. The differences in bone metabolism between rodents and primates likely explain why the high incidence of osteosarcomas observed in rats has not been observed in monkeys and in humans. A limited number of monkeys have been exposed to abaloparatide during the development programme at doses up to 70 µg/kg (with a protocol defined reduction to 50 µg/kg) for 39 weeks and 5 µg/kg for 16 months. In these studies, no neoplasms were noted.

Important potential risk 1: Osteosarcoma	
	Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of abaloparatide. The relevance of these rat findings to humans is uncertain, thus the use of abaloparatide should be avoided for patients at increased risk of osteosarcoma. During the post-marketing surveillance, no cases of osteosarcoma have been reported with abaloparatide treatment and no increase in the incidence of osteosarcoma has been identified with teriparatide treatment in the post-marketing studies.
Risk factors and risk groups	In elderly patients, osteosarcoma is often considered a secondary neoplasm attributed to the sarcomatous transformation of Paget's disease of bone (Mirabello, Troisi, & Savage, 2009). Exposures to radiation therapy, alkylating agents, could increase the chance of secondary osteosarcoma (Mirabello, 2009; Wu, 2012).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and in PL section 2 indicate that abaloparatide should not be used in children and adolescents less than 18 years because of safety concerns. SmPC section 4.3 and in PL section 2 include contraindications to the use of the product in the following situations: patients with unexplained elevations of serum alkaline phosphatase; patients with known risks for osteosarcoma such as those who have received prior external beam or implant radiation therapy involving the skeleton; patients with skeletal malignancies or bone metastases. SmPC section 4.4 and PL section 3 states that the maximum duration of treatment with abaloparatide should be 18 months and includes an additional statement that an increased risk of osteosarcoma was observed in rats following long-term administration of abaloparatide. SmPC section 5.3 includes preclinical safety data from a 2-year rat carcinogenicity study related to osteosarcoma. Legal status: Prescription only medicine. Additional risk minimisation measures: None

Important potential risk 2: Serious cardiovascular events (i. e. MACE, arrhythmia)	
Evidence for linking the risk to the medicine	The prevalence of palpitations in elderly (60 to 94 years) has been reported as 8.3% (Lok, 1996). Transient increase in heart rate may occur with abaloparatide, which may resolve in few hours. In women with postmenopausal osteoporosis, adverse reactions of tachycardia, including sinus tachycardia, were reported in 1.6% of patients receiving abaloparatide and 0.4% of patients in the placebo group. In the QT/QTc study, abaloparatide has been associated with a dose-dependent increase in heart rate which developed within 15 minutes after injection and resolved in about 6 hours.

Important potential risk 2: Serious cardiovascular events (i. e. MACE, arrhythmia)	
	Although, abaloparatide treatment did not increase the risk of having a serious cardiovascular event (i.e. MACE, arrhythmia), the potential exists due to abaloparatide causing transient increase in heart rate.
Risk factors and risk groups	Patients with significant cardiovascular disease may be at increased risk of cardiac events.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 PL section 4. SmPC section 4.2 and PL section 3 include a statement about the appropriate administration. SmPC section 4.4 and PL section 2 include warnings for orthostatic hypotension and increased heart rate describing the risk, measures to be assessed prior to beginning abaloparatide treatment and instruction for monitoring potential adverse events and action to be taken in case they occur. SmPC Section 4.5 and PL section 2 include a statement about the concomitant medication affecting blood pressure. SmPC section 4.9 and PL section 3 include palpitations and orthostatic hypotension as effects of abaloparatide overdose that might be expected. SmPC section 5.3 describes the cardiovascular results from a safety pharmacology study. Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Abaloparatide PASS: European non-interventional PASS to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide .

Missing information:

None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Eladynos 80 micrograms/dose solution for injection in pre-filled pen.