Summary of risk management plan for Macimorelin Aeterna Zentaris (macimorelin)

This is a summary of the risk management plan (RMP) for Macimorelin Aeterna Zentaris. The RMP details important risks of Macimorelin Aeterna Zentaris, how these risks can be minimised, and how more information will be obtained about Macimorelin Aeterna Zentaris risks and uncertainties (missing information).

Macimorelin Aeterna Zentaris summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Macimorelin Aeterna Zentaris should be used.

This summary of the RMP for Macimorelin Aeterna Zentaris 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 Macimorelin Aeterna Zentaris RMP.

I. The medicine and what it is used for

Macimorelin Aeterna Zentaris is authorised for the diagnosis of growth hormone deficiency (GHD) in adults. It contains macimorelin acetate as the active substance and it is given as oral suspension. The recommended single oral dose is defined as 0.5 mg macimorelin per kg body weight.

Further information about the evaluation of Macimorelin Aeterna Zentaris benefits can be found in Macimorelin Aeterna Zentaris 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/macimorelin-aeterna-zentaris.

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

Important risks of Macimorelin Aeterna Zentaris, together with measures to minimise such risks and the proposed studies for learning more about Macimorelin Aeterna Zentaris 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 continuously collected and regularly analysed, including 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 Macimorelin Aeterna Zentaris is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Macimorelin Aeterna Zentaris 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 Macimorelin Aeterna Zentaris. 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	Torsade de pointes
	False positive diagnosis of growth hormone deficiency in patients with BMI > 40 kg/m^2, and in those receiving concomitant CYP3A4 inducers
Missing information	Usefulness of the test during pregnancy and safety for the unborn child during pregnancy

II.B Summary of important risks

Torsade de pointes (important potential risk 1)	
Evidence for linking the risk to the medicine	During clinical development, two transient ECG abnormalities were observed in one test subject and reported as serious possibly adverse reactions. These ECG abnormalities consisted of T wave abnormalities and QT prolongation. Macimorelin causes an increase of about 11 ms in the corrected QT (Qtc) interval (see also SmPC section 5.1). QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases. Due to the QT prolongation as described during the clinical development of macimorelin and depending on the actual mechanism, the EMA recommended during the D120 LoQ process to consider the inclusion of Torsade de pointes as a safety concern in the RMP.

Risk factors and risk groups	Patients with proarrhythmic condition (e.g., history of myocardial infarction, heart failure or prolonged ECG QTc interval, defined as QTc > 500 ms) are considered as patients at risk. For such patients, ECG controls may be indicated prior to the administration of macimorelin and 1 hour, 2 hours, 4 hours and 6 hours after administration of macimorelin. In patients with known congenital or acquired long QT syndrome and in patients with a history of torsades de pointes, the use of Macimorelin may only be considered in a cardiovascular clinical unit. In addition to patient inherent risk factors, also the Co-administration of macimorelin with medicinal products with a potential to induce torsades de pointe (antipsychotic medicinal products e.g. chlorpromazine, haloperidol, thioridazine, ziprasidone, such as antibiotics e.g. moxifloxacin, erythromycin, clarithromycin, anti-arrhythmics such as Class Ia e.g. quinidine, procainamide and Class III antiarrhythmic medications e.g. amiodarone, sotalol or any other medicinal products known to induce torsades de pointe) should be avoided.
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4 SmPC section 4.5 SmPC section 5.1 PL section 2 Pack size Restricted medical prescription <Additional risk minimisation measures> Not applicable

False positive diagnosis of growth hormone deficiency in patients with BMI > 40 kg/m², and in those receiving concomitant CYP3A4 inducers (important potential risk 2)	
Evidence for linking the risk to the medicine	Macimorelin is indicated for the diagnosis of growth hormone deficiency (GHD) in adults. Clinical studies have established that a maximally stimulated serum GH level of less than 2.8 ng/mL (at the 45, 60 or 90 minute timepoints) following macimorelin administration confirms a diagnosis of adult growth hormone deficiency. However, the results should always be interpreted in the context of the overall clinical presentation and on the basis of two independently conducted GH stimulation tests.

	Safety and diagnostic performance have not been established for subjects with BMI > 40 kg/m^2. Based on the characteristics of the substance and its target, strong CYP3A4 inducers as concomitant medication could have an impact on the outcome of the test. Furthermore, medical conditions affecting the hypothalamic-pituitary axis could also lead to false test outcomes.
Risk factors and risk groups	As risk factors for potential lack of efficacy, the following are defined: - concomitant intake of strong CYP3A4 inducers - BMI > 40° kg/m²
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.4 SmPC section 4.5 PL section 2 Pack size Restricted medical prescription <Additional risk minimisation measures> Not applicable

Usefulness of the test during pregnancy and safety for the unborn child during pregnancy (missing information 1)	
Risk minimisation measures	<Routine risk minimisation measures> SmPC section 4.6 SmPC section 5.3 PL section 2 Pack size Restricted medical prescription <Additional risk minimisation measures> Not applicable

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 Macimorelin Aeterna Zentaris.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Macimorelin Aeterna Zentaris.