

Part VI: Summary of the risk management plan

Summary of risk management plan for PLENADREN (hydrocortisone)

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

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

This summary of the RMP for PLENADREN 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 PLENADREN's RMP.

I. The medicine and what it is used for

PLENADREN is authorised for the treatment of adrenal insufficiency in adults. It contains hydrocortisone as the active substance and it is given by oral route as 5 mg and 20 mg modified-release tablets.

Further information about the evaluation of PLENADREN's benefits can be found in PLENADREN's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/human/EPAR/plenadren>

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

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

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

- (a)** Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- (b)** Important advice on the medicine's packaging;
- (c)** The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- (d)** 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/PBRER 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 PLENADREN is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of PLENADREN are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 PLENADREN. 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	Cortisol deficiency-related symptoms after change from immediate release hydrocortisone
Important potential risks	Glucocorticoid under-replacement Glucocorticoid over-replacement Glucocorticoid under- or over-replacement due to drug-drug interactions Off-label use in children and adults
Missing information	Pregnancy and lactation Hepatic impairment Renal impairment Gastrointestinal emptying or motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility Paediatric subjects

II.B Summary of important risks

Important identified risk: Cortisol deficiency-related symptoms after change from immediate release hydrocortisone	
Evidence for linking the risk to the medicine	The highest frequency of cortisol deficiency-related AEs was observed in the beginning of the PLENADREN treatment period (weeks 0–4) when 13% of the patients reported any such AE compared to 8% during weeks 0–4 on t.i.d. treatment. The pattern of higher frequency of AEs assessed as possibly cortisol deficiency-related initially after change was observed also in the newly recruited patients in Study DC 08/01 with 5 of the possibly cortisol deficiency-related AEs reported by 5 newly recruited patients (31%) and 17 AEs reported by 13 patients recruited from Study DC 06/02 (24%) from 0 to 6 months.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and 4.8 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Important potential risk: Glucocorticoid under-replacement

Evidence for linking the risk to the medicine	Clinical studies
Risk factors and risk groups	No clear risk group was identified in terms of MR-HC's propensity to cause under replacement.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Important potential risk: Glucocorticoid over-replacement	
Evidence for linking the risk to the medicine	Clinical studies
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Important potential risk: Glucocorticoid under- or over-replacement due to drug-drug interactions	
Evidence for linking the risk to the medicine	No clinical drug-drug interaction studies have been performed to date with PLENADREN. Theoretical drug-drug interactions that are associated with the hydrocortisone class of glucocorticoid drugs are listed in the SmPC based on a literature review of pharmacological doses of hydrocortisone.
Risk factors and risk groups	Unknown. The Clinical Study Programme has not demonstrated any drug interactions with either potent CYP3A4 inducers or inhibitors during treatment with MR-HC.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 Additional risk minimisation measures:

	None.
Additional pharmacovigilance activities	None.

Important potential risk Off-label use in children and adults	
Evidence for linking the risk to the medicine	Post marketing reports
Risk factors and risk groups	MR-HC is currently not indicated in children in the EU. Off label use in children and/or adolescents with CAH cannot be excluded as currently o.d. glucocorticoid replacement therapy for this disease does not exist. Off label use in adults cannot be fully excluded for layman concepts such as 'adrenal fatigue'. However, as this is not a medically recognised condition the risk for off label use in adults is considered very low as MR-HC is a prescription drug.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.1 and 4.2 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Missing information: Pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

Missing information: Hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2 Additional risk minimisation measures: None.

Additional pharmacovigilance activities	None.
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Missing information: Renal impairment	
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC Sections 4.2 and 5.2</p> <p>Additional risk minimisation measures: None.</p>
Additional pharmacovigilance activities	None.

Missing information: Gastrointestinal emptying or motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility	
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC Sections 4.4 and 4.5</p> <p>Additional risk minimisation measures: None.</p>
Additional pharmacovigilance activities	None.

Missing information: Paediatric subjects	
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC Section 4.2 that the safety and efficacy of Plenadren in children/adolescents aged below 18 years have not yet been established. No data are available.</p> <p>Additional risk minimisation measures: None.</p>
Additional pharmacovigilance activities	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 PLENADREN.

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

There are no studies required for PLENADREN.

