# Swiss Summary of the Risk Management Plan (RMP) for Hydrocortisone (PLENADREN)

Version 2.0, 24-Nov-2023
Based on EU RMP version 4.0, 21-Jun-2023
Marketing Authorization Holder: Takeda Pharma AG

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 risk as well as to prevent or minimise them.

The RMP summary of PLENADREN 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 PLENADREN in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of PLENADREN.

# Summary of activities in the 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

risksImportant 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 packageleaflet 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 themedicine is used correctly;

(d) The medicine's legal status — the way a medicine is supplied to the patient (e.g. with orwithout 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<br>• Glucocorticoid over-replacement<br>• Glucocorticoid under- or over-replacement due to drug-drug interactions<br>• Off-label use in children and adults |
| Missing information | • Pregnancy and lactation<br>• Hepatic impairment<br>• Renal impairment<br>• Gastrointestinal emptying or motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility<br>• 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 minimization measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2 and 4.8<br>**Additional risk minimisation measures:**<br>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 minimization measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.2, 4.4, and 4.8<br>**Additional risk minimisation measures:**<br>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 minimization measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.2 and 4.4.<br>**Additional risk minimisation measures:**<br>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 minimization measures | **Routine risk minimisation measures:**<br>SmPC Section 4.5<br>**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 minimization measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.1 and 4.2<br>**Additional risk minimisation measures:**<br>None. |
| Additional pharmacovigilance activities | None. |

| **Missing Information: Pregnancy and lactation** | |
|---|---|
| Risk minimization measures | **Routine risk minimisation measures:**<br>SmPC Section 4.6<br>**Additional risk minimisation measures:**<br>None. |
| Additional pharmacovigilance activities | None. |

| **Missing Information: Hepatic impairment** | |
|---|---|
| Risk minimization measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.2 and 5.2<br>**Additional risk minimisation measures:**<br>None. |
| Additional pharmacovigilance activities | None. |

| **Missing Information: Renal impairment** | |
|---|---|
| Risk minimization measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.2 and 5.2<br>**Additional risk minimisation measures:**<br>None. |
| Additional pharmacovigilance activities | None. |

| **Missing Information: Gastrointestinal emptying or motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility** | |
|---|---|
| Risk minimization measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.4 and 4.5<br>**Additional risk minimisation measures:**<br>None. |
| Additional pharmacovigilance activities | None. |

| **Missing Information: Paediatric subjects** | |
|---|---|
| Risk minimization measures | **Routine risk minimisation measures:**<br>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.<br>**Additional risk minimisation measures:**<br>None. |
| 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.