VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

PLENADREN contains hydrocortisone and is used to treat adrenal insufficiency (AI) in adults. AI occurs when the adrenal glands (just above the kidneys) do not produce enough of the hormone cortisol. Cortisol is essential both for the everyday wellbeing and the ability to handle stressful situations, which includes both psychological and physiological stress such as infections and other diseases. Therefore patients with AI need to be treated with hydrocortisone to replace the cortisol not produced by the body. AI can be primary or secondary. Primary AI is called Addison's disease and happens when there is disease in the adrenal glands. Secondary AI occurs due to disease in the pituitary gland (a pea-sized gland at the base of the brain). A pituitary tumour is the main cause of secondary AI. Secondary AI is more common than primary AI. Primary AI or Addison's disease affects approximately 117 of every 1 million people, and secondary AI affects about 215 of every 1 million people. AI may develop slowly, or it can be sudden and life-threatening with severe salt and water shortage, which can lead to shock and death if not treated.

VI.2.2 Summary of Treatment Benefits

PLENADREN replaces the natural cortisol that is missing in AI. The tablet has been modified in order to delivers hydrocortisone to your body throughout the day, as opposed to other hydrocortisone preparations which are more short-acting and needs to be taken twice or thrice daily. The cortisol level in your blood increases rapidly to a maximum level, about 1 hour after taking the tablet in the morning, and then gradually decreases over the day with no or almost no cortisol level in the blood in the late evening and night when the levels should be low. In clinical studies, PLENADREN led to improvements in patients with AI alone, and in those who also had diabetes mellitus, compared with immediate release hydrocortisone. When hydrocortisone is given to replace the cortisol which should have been produced by the body, side effects may occur such as weight increase and high blood pressure. In one of the main studies in patients with primary AI, PLENADREN treatment resulted in favourable changes in body weight, blood pressure, blood sugar, cholesterol levels ('good cholesterol') and bone health, compared with short-acting hydrocortisone. Long-term PLENADREN treatment has also shown improvements in body weight, blood pressure and blood sugar, following 18 months' treatment.

VI.2.3 Unknowns Relating to Treatment Benefits

Patients with severe kidney or liver disease, or gastrointestinal emptying disorders, and children and women who were pregnant or breastfeeding were not included in the main and supporting studies. Caution is recommended in these patients and PLENADREN should always be taken in accordance with the SmPC.

VI.2.4 Summary of Safety Concerns

Table 1: Important Identified Risks

Risk	What is Known	Preventability
Symptoms related to shortage of the hormone cortisol after changing from short-acting hydrocortisone (cortisol deficiency-related symptoms after change from immediate release hydrocortisone)	In clinical studies there was an increase in the number of side effects during the first 8 weeks after changing from short-acting hydrocortisone tablets to PLENADREN. The side effects were fatigue, nausea, upper abdominal pain, and diarrhoea. These side effects were mild or moderate, and lasted a short time.	This risk can be reduced by monitoring the patient and changing the dose if needed.

Table 2: Important Potential Risks

Risk	What is Known (Including reason why it is considered a potential risk)
Using too low a dose of PLENADREN (glucocorticoid under-replacement)	The signs of too low a dose such as feeling tired and stomach symptoms are easy to observe and disappear immediately when the dose is increased.
Using too high a dose of PLENADREN (glucocorticoid over-replacement)	A too high a dose of PLENADREN may be harmful. It can cause blood pressure to increase, weight gain and blood sugar may become too high.
Glucocorticoid under- or over-replacement due to drug-drug interactions	PLENADREN and other medicines can affect each other and lead to too high or too low hydrocortisone levels, which may increase the risk of side effects.
Use of the medicine in a way that is not covered by the medicine's product information (off-label use in children and adults)	This medicine has not been studied in patients under 18 years of age.

Table 3: Missing Information

Risk	What is Known
Pregnancy and breast-feeding (pregnancy and lactation)	Patients should continue treatment with PLENADEN during pregnancy. PLENADREN treatment in pregnant women with AI is unlikely to cause any harmful effects on the mother and/or the baby. Patients can breast-feed during PLENADREN treatment. Hydrocortisone is removed from the body in breast milk. Doses of hydrocortisone used for replacement therapy are unlikely to have any effect on the child.
Reduced liver function (hepatic impairment)	This medicine has not been studied in patients with severe reduced liver function. Therefore dose adjustments may be needed in these patients.
Reduced kidney function (renal impairment)	This medicine has not been studied in patients with severe reduced kidney function. Therefore dose adjustments may be needed in these patients.
Abnormal stomach emptying (gastrointestinal emptying or	There is no information on the use of PLENADREN in patients with abnormal stomach emptying.

Table 3: Missing Information

Risk	What is Known
motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility)	
Children (paediatric subjects)	PLENADREN has not been studied in children and adolescents under 18 years of age.

AI=adrenal insufficiency.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a SmPC that provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, the risks, and the recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The SmPC and the package leaflet for PLENADREN can be found in the PLENADREN EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned Post Authorisation Development Plan

Table 4: List of Studies in Post-authorisation Development Plan

Study/Activity (including study number)	Objectives	Safety Concerns/Efficacy Issue Addressed	Status	Planned Date for Submission of (Interim and) Final Results
SHP617-400 (EU-AIR): a European multi-centre, multi-country, post-authorisation, observation study (registry) of patients with chronic adrenal insufficiency Category 3	To monitor the safety of long-term treatment with PLENADREN modified-release tablet and other glucocorticoid replacement therapies in patients with chronic AI with a focus on: - Intercurrent illness - Adrenal crisis - SAEs	Cortisol deficiency-related symptoms after change from immediate release hydrocortisone Glucocorticoid under-replacement Glucocorticoid over-replacement Glucocorticoid under- or over-replacement due to drug-drug interactions Off-label use in children and adults Pregnancy and lactation Hepatic impairment Renal impairment Gastrointestinal emptying or motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility Paediatric subjects Elderly subjects Long-term safety Mortality	Ongoing	Summary of safety information collected will be presented annually in the PBRER. Interim analysis (when 900 patient-years for Plenadren arm are reached). The decision to discontinue the analysis will be agreed between the Sponsor and the CHMP

CHMP=Committee for Medicinal Products for Human Use; PBRER=periodic benefit-risk evaluation report; SAEs=serious adverse events.

VI.2.6.1 Studies which are a Condition of the Marketing Authorisation

None of the above studies are conditions of the marketing authorisation.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 5: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
2.4	At time of authorisation 03 Nov 2011	**Identified risks** Cortisol deficiency-related symptoms after change from immediate release	

Table 5: Major Changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
		hydrocortisone **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 Elderly subjects Long-term safety Mortality	
2.5	09 Dec 2013	Same as version 2.4	RMP submitted with final SHP617-404 (SWE-DUS) protocol

Table 5: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
3.0	At the time of EU renewal	**Identified risks** Cortisol deficiency-related symptoms after change from immediate release hydrocortisone **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	The RMP was reformatted to comply with the requirements of the new EU RMP template (dated 25 Jul 2013) Based on the completion of SHP617-301 (DC 08/01) 'elderly subjects', 'long-term safety' and 'mortality' removed as missing information
3.1	23 Jan 2017	Same as version 3.0	SHP617-404 (SWE-DUS) removed from the RMP
3.2	13 Sep 2017	Drug-drug interactions changed to Glucocorticoid under- or over-replacement due to drug-drug interactions Otherwise same as version 3.1	

EU=European Union; RMP=Risk Management Plan