ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Plenadren 5 mg modified-release tablets
Plenadren 20 mg modified-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Plenadren 5 mg modified-release tablets
Each modified-release tablet contains hydrocortisone 5 mg.

Plenadren 20 mg modified-release tablets
Each modified-release tablet contains hydrocortisone 20 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablet.

Plenadren 5 mg modified-release tablets
The tablets are round (diameter 8 mm), convex and pink.

Plenadren 20 mg modified-release tablets
The tablets are round (diameter 8 mm), convex and white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adrenal insufficiency in adults.

4.2 Posology and method of administration

Posology

Plenadren is given as maintenance therapy. Oral replacement doses must be individualised according to the clinical response. A common maintenance dose is 20–30 mg per day, given once daily in the morning. In patients with some remaining endogenous cortisol production a lower dose may be sufficient. 40 mg is the highest maintenance dose studied. The lowest possible maintenance dosage should be used. In situations when the body is exposed to excessive physical and/or mental stress, patients may need additional substitution of immediate release hydrocortisone tablets especially in the afternoon/evening, see also section 'Use in intercurrent illness' where other ways of temporarily increasing the dose of hydrocortisone is described.

Changing from conventional oral glucocorticoid treatment to Plenadren
When changing patients from conventional oral hydrocortisone replacement therapy given three times daily to Plenadren, an identical total daily dose may be given. Due to a lower bioavailability of the daily dose of Plenadren compared to that of conventional hydrocortisone tablets given three times daily (see section 5.2) clinical response needs to be monitored and further dose individualisation may be required. Changing patients from hydrocortisone tablets given twice daily, cortisone acetate or synthetic glucocorticoids to Plenadren has not been studied, but changing to a hydrocortisone equivalent daily dose of Plenadren is recommended in these instances; further dose individualisation may be required.

Use in intercurrent illness
During intercurrent illness, there should be high awareness of the risk of developing acute adrenal insufficiency.

In severe situations, an increase in dose is immediately required and oral administration of hydrocortisone must be replaced with parenteral, preferably intravenous treatment. Intravenous administration of hydrocortisone is warranted during transient illness episodes such as severe infections, in particular gastroenteritis associated with vomiting and/or diarrhoea, high fever of any aetiology or extensive physical stress, such as for instance serious accidents and surgery under general anaesthesia, see section 4.4.

In less severe situations when intravenous administration of hydrocortisone is not required, for instance low grade infections, fever of any aetiology and stressful situations such as minor surgical procedures, the normal oral daily replacement dose must be increased temporarily; the total daily dose should be increased by administering the maintenance dose twice or thrice daily with 8 ±2 hours intervals (an increase in number of administrations, not increasing the morning dose). This regimen has been documented in over 300 intercurrent illness episodes within the clinical study programme. At the discretion of the treating physician, immediate release hydrocortisone tablets can be given instead of Plenadren or may be added to treatment. Increasing the dose of hydrocortisone at one dose occasion increases the total plasma exposure of cortisol less than proportional, see section 5.2. Once the intercurrent illness episode is over, patients can return to the normal maintenance dose.

Special populations

Elderly
In case of age-related low body weight, monitoring of the clinical response is recommended and dose adjustment to a lower dose may be required, see section 5.2.

Renal impairment
There is no need for dosage adjustment in patients with mild to moderate renal impairment. In patients with severe renal impairment monitoring of the clinical response is recommended and dose adjustment may be required, see section 5.2.

Hepatic impairment
There is no need for dose adjustment in mild to moderate hepatic impairment. In case of severe hepatic impairment, the functional liver mass decreases and thus the metabolising capacity for hydrocortisone. Therefore, monitoring of the clinical response is recommended and dose adjustment may be required, see section 5.2.

Paediatric population
The safety and efficacy of Plenadren in children/adolescents aged below 18 years have not yet been established. No data are available.

Method of administration
Patients should be instructed to take Plenadren orally with a glass of water on awakening at least 30 minutes before food intake, preferably in an upright position and between 6.00 am and 8.00 am in the morning. It should be swallowed whole; tablets should not be divided, chewed or crushed. If more than one daily administration is required the morning dose should be given as instructed, additional doses given later during the day can be given with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Acute adrenal insufficiency
Acute adrenal insufficiency may develop in patients with known adrenal insufficiency who are on inadequate daily doses or in situations with increased cortisol need. Events have been reported in patients treated with Plenadren. Adrenal crisis can develop in patients with acute adrenal insufficiency. Therefore, patients should be advised of the signs and symptoms of acute adrenal insufficiency and of adrenal crisis and the need to seek immediate medical attention.

During adrenal crisis parenteral, preferably intravenous administration of hydrocortisone in high doses, together with sodium chloride 9 mg/ml (0.9%) solution for infusion, should be administered according to current treatment guidelines.

Concomitant infections
During transient illnesses such as low grade infection, fever of any aetiology, stressful situations such as minor surgical procedures, the daily replacement dose must be increased temporarily, see section 4.2, 'Use in intercurrent illness'. The patient must be carefully informed how to act in these situations and also advised to immediately seek medical attention should an acute deterioration occur; especially in cases of gastroenteritis, vomiting and/or diarrhoea leading to fluid and salt loss, as well as to inadequate absorption of oral hydrocortisone.

Patients with adrenal insufficiency and concomitant retroviral infection, such as HIV, need careful dose adjustment due to potential interaction with antiretroviral medicinal products and increased hydrocortisone dose due to the infection.

Scientific reports do not support immunosuppressive effects of hydrocortisone in doses that have been used for replacement therapy in patients with adrenal insufficiency. Therefore, there is no reason to believe that replacement doses of hydrocortisone will exacerbate any systemic infection or worsen the outcome of such an infection. Moreover, there is no reason to believe that doses of hydrocortisone used for replacement therapy in adrenal insufficiency may reduce the response to vaccines and increase the risk of generalised infection with live vaccines.

Gastric emptying and motility disorders
Modified-release tablets are not recommended in patients with increased gastrointestinal motility, i.e., chronic diarrhoea, due to the risk of impaired cortisol exposure. There are no data in patients with confirmed slow gastric emptying or decreased motility disease/disorder. The clinical response should be monitored in patients with these conditions.

Using higher than normal doses of hydrocortisone
High (supra-physiological) dosages of hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Long-term treatment with higher than physiological hydrocortisone doses can lead to clinical features resembling Cushing´s syndrome with increased adiposity, abdominal obesity, hypertension and diabetes, and thus result in an increased risk of cardiovascular morbidity and mortality.

Old age and low body mass index are known risk factors for common adverse reactions of pharmacological doses of glucocorticoids such as osteoporosis, thinning of skin, diabetes mellitus, hypertension and increased susceptibility to infections.

All glucocorticoids increase calcium excretion and reduce the bone-remodelling rate. Patients with adrenal insufficiency on long-term glucocorticoid replacement therapy have been found to have reduced bone mineral density.

Prolonged use of high doses of glucocorticoids may produce posterior subcapsular cataracts, and glaucoma with possible damage to the optic nerves. Such effects have not been reported in patients receiving replacement therapy with glucocorticoids in doses used in adrenal insufficiency.

Psychiatric adverse reactions may occur with systemic glucocorticoids. This may occur during commencement of treatment and during dose adjustments. Risks may be higher when high doses are given. Most reactions resolve after dose reduction, although specific treatment may be necessary.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

Thyroid function
Patients with adrenal insufficiency should be monitored for thyroid dysfunction as both hypothyroidism and hyperthyroidism may markedly influence the exposure of administered hydrocortisone.

Treatment of primary adrenal insufficiency often warrants addition of a mineralocorticoid.

4.5 Interaction with other medicinal products and other forms of interaction

Hydrocortisone interactions listed below have been reported after therapeutic doses of glucocorticoids.

Potent CYP 3A4 inducers such as phenytoin, rifabutin, carbamazepine, barbiturates, rifampicin, St. John's wort and less potent inducers such as the antiretroviral medicinal products efavirenz and nevirapine can enhance the metabolic clearance of cortisol, decrease terminal half-life and thus reduce circulating levels and increase fluctuations of cortisol (due to shorter terminal half-life). This may require dose adjustment of hydrocortisone.

Potent CYP 3A4 inhibitors such as ketoconazole, itraconazole, posaconazole, voriconazole erythromycin, telithromycin, clarithromycin, ritonavir and grapefruit juice can inhibit the metabolism of hydrocortisone, and thus increase blood levels. During long-term prophylactic treatment with any of the antibiotics, adjustment of the hydrocortisone dosage should be considered.

The effect of corticosteroids may be reduced for 3-4 days after treatment with mifepristone.

The clinical response needs to be monitored in patients given medicinal products affecting gastric emptying and motility, see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
Plenadren can be used during pregnancy. There is no indication that hydrocortisone replacement therapy in pregnant women with adrenal insufficiency is associated with adverse outcome of the mother and/or the foetus. Untreated adrenal insufficiency during pregnancy is associated with poor outcome of both the mother and the foetus, therefore it is important to continue treatment during pregnancy.

Reproductive studies in animals have shown that glucocorticoids can cause foetal abnormalities and reproductive toxicity, see section 5.3.

The dose of hydrocortisone should be carefully monitored during pregnancy in women with adrenal insufficiency. Dosing according to individual clinical response is recommended.

Breast-feeding
Hydrocortisone is excreted in breast milk. Plenadren can be used during breast-feeding. Doses of hydrocortisone used for replacement therapy are unlikely to have any clinically significant impact on the child. Infants of mothers taking high doses of systemic glucocorticoids for prolonged periods may be at risk of adrenal suppression.

Fertility
Patients with adrenal insufficiency have been shown to have reduced parity, which is most likely due to the underlying disease, but there is no indication that hydrocortisone in doses for replacement therapy will affect fertility.

4.7 Effects on ability to drive and use machines

Plenadren has minor influence on the ability to drive and use machines. Fatigue and episodes of short-lasting vertigo have been reported.

Untreated and poorly replaced adrenal insufficiency may affect the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Hydrocortisone is given as replacement therapy aimed at restoring normal cortisol levels. The adverse reaction profile in the treatment of adrenal insufficiency is therefore not comparable to that in other conditions requiring much higher doses of oral or parenteral glucocorticoids.

Overall, the frequency and type of adverse reactions were similar for Plenadren once daily modified-release tablets and hydrocortisone tablets given three times daily in a 12-week study. There was an initial increase in the frequency of adverse reactions in about one in five patients, observed up to eight weeks after first changing from conventional hydrocortisone tablets given three times daily to once daily modified-release tablets. However, these adverse reactions (abdominal pain, diarrhoea, nausea and fatigue) are mild or moderate, transient, of short duration but may require dose adjustment or additional concomitant medicinal products, see section 4.2. Fatigue has been reported as very common.

Tabulated list of adverse reactions
A total of 80 patients (173 patient-years of data) have been treated with modified-release hydrocortisone in clinical studies. Adverse reactions from these studies and from postmarketing surveillance are listed below by system organ class and frequency as follows:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10).

MedDRA System Organ Class	Frequency of adverse reactions	
	Very common	Common
Nervous system disorders	Vertigo Headache	
Gastrointestinal disorders	Diarrhoea	Upper abdominal pain Nausea
Skin and subcutaneous tissue disorders		Pruritus Rash
Musculoskeletal and connective tissue disorders		Arthralgia
General disorders and administration site conditions	Fatigue	

In addition the following adverse reactions have been reported for other hydrocortisone medicinal products given for indications other than adrenal insufficiency replacement therapy in higher doses (frequencies not known).

Immune system disorders
Activation of infection (tuberculosis, fungal and viral infections including herpes).

Endocrine disorders
Induction of glucose intolerance or diabetes mellitus.

Metabolism and nutrition disorders
Sodium and water retention and oedema tendency, hypertension, hypokalaemia.

Psychiatric disorders
Euphoria and psychosis, insomnia.

Eye disorders
Increased intraocular pressure and cataract.

Gastrointestinal disorders
Dyspepsia and deterioration of existing gastric ulcer.

Skin and subcutaneous tissue disorders
Cushing-like symptoms, stria, ecchymoses, acne and hirsutism, impaired wound healing.

Musculoskeletal and connective tissue disorders
Osteoporosis with spontaneous fractures.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Reports of acute toxicity and/or deaths following hydrocortisone overdose are rare. No antidote is available. Symptoms may range from excitement/arousal to mania or psychosis. Signs include high blood pressure, elevated plasma glucose levels and hypokalaemia. Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him/her unusually susceptible to ill effects from hydrocortisone. In which case, symptomatic treatment should be instituted as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, glucocorticoids, ATC code: H02AB09

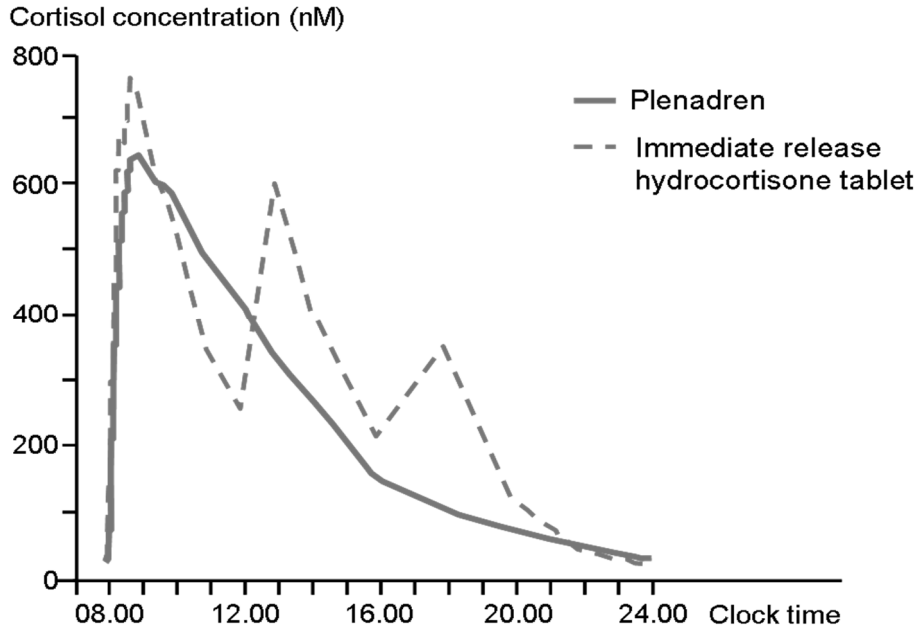
Pharmacodynamic effects
Hydrocortisone is a glucocorticoid and the synthetic form of endogenously produced cortisol. Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue and the brain. Cortisol is the principal glucocorticoid secreted by the adrenal cortex.

Naturally-occurring glucocorticoids (hydrocortisone and cortisol), which also have salt-retaining properties, are used as replacement therapy in adrenal insufficiency. They are also used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition they modify the body's immune responses to diverse stimuli.

Clinical efficacy
The pivotal study was a randomised, two-period 12-week crossover multi-centre trial in 64 patients with primary adrenal insufficiency, 11 of whom had concomitant diabetes mellitus and 11 had hypertension. The study compared modified-release tablets given once daily with conventional tablets given three times daily using the same daily dose of hydrocortisone (20 to 40 mg).

Compared to conventional tablets given three times daily, once daily modified-release tablets resulted in an increased cortisol exposure during the first four hours after intake in the morning but reduced exposure in the late afternoon/evening and over the 24-hour period (Figure 1).

Figure 1. Observed mean serum cortisol concentration versus clock time following single and multiple dosing in primary adrenal insufficiency patients (n=62) after oral administration of Plenadren given once daily and hydrocortisone thrice daily.



5.2 Pharmacokinetic properties

Absorption

Following oral administration, hydrocortisone is rapidly and well absorbed from the gastrointestinal tract and the absorption has been reported to be more than 95% for an oral 20 mg dose (tablets). Hydrocortisone is a class II active substance according to the biopharmaceutical classification system (BCS) with a high intestinal permeability and a low dissolution rate, especially at higher doses. The modified-release tablet has an outer coating layer that provides an immediate release of the drug and an extended release core. The immediate-release part provides a rapid onset of absorption and the extended-release part provides a more extended plasma profile of cortisol. The bioavailability ($AUC_{0\text{-}24h}$) is 20% lower with the modified-release tablet compared to the same daily dose of hydrocortisone given as conventional tablets three times daily. When the oral dose is increased the total plasma exposure of cortisol increased less than proportional. The exposure increased three-fold when the dose of hydrocortisone modified-release increased from 5 mg to 20 mg.

The absorption rate of hydrocortisone was reduced after food intake resulting in a delay in the time to maximal concentration in plasma from on average less than 1 hour to over 2.5 hours. On the other hand, the extent of absorption and bioavailability was approximately 30% higher for the 20 mg tablet after food intake compared to fasting and there was no absorption failure or dose dumping.

Distribution

In plasma, cortisol is bound to corticosteroid-binding globulin (CBG, also called transcortin) and albumin. The binding is about 90%.

Elimination

The terminal half-life has been reported to be about 1.5 hours following intravenous and oral dosing of hydrocortisone tablets. The terminal half-life of cortisol following administration of Plenadren was

about 3 hours and formulation release controlled. This terminal half-life is similar to the pharmacokinetics of endogenous cortisol that also is secretion-controlled.

Hydrocortisone (cortisol) is a lipophilic drug that is eliminated completely via metabolism with a low clearance and accordingly low intestinal and hepatic extraction ratios.

Hydrocortisone is eliminated completely by metabolism by 11ßHSD type 1 and type 2 enzymes and CYP 3A4 in the liver and in peripheral tissue. CYP 3A4 is involved in the clearance of cortisol by the formation of 6β-hydroxycortisol which is excreted in urine. The transport of cortisol across membranes is expected to be mediated mainly by passive diffusion and therefore renal and biliary clearances are negligible.

Special populations

Renal impairment
A small amount of cortisol is excreted in the urine unchanged (<0.5% of the daily production), meaning that cortisol is eliminated completely by metabolism. Since severe renal impairment may affect medicinal products completely eliminated via metabolism, dose adjustment may be needed.

Hepatic impairment
No study has been performed in patients with hepatic impairment, however data in the literature for hydrocortisone support that no dose adjustment is required in mild to moderate hepatic impairment. In case of severe hepatic impairment, the functional liver mass decreases and thus the metabolising capacity for hydrocortisone. This may require dose individualisation.

Paediatric population
No pharmacokinetic data are available in children or adolescents.

5.3 Preclinical safety data

Animal experiments have shown that prenatal exposure to very high doses of glucocorticoids can induce malformations (cleft palate, skeletal malformations). Animal studies have also shown that prenatal exposure to high doses of glucocorticoids (but lower than teratogenic doses) may be associated with increased risk of intrauterine growth retardation, cardiovascular disease in adulthood and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose
Microcrystalline cellulose
Pregelatinised starch (maize)
Colloidal, anhydrous silica
Magnesium stearate

Tablet coating

Plenadren 5 mg modified-release tablets
Macrogol (3350)
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Iron oxide red (E172)

Iron oxide yellow (E172)
Iron oxide black (E172)

Plenadren 20 mg modified-release tablets
Macrogol (3350)
Polyvinyl alcohol
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with PP screw cap containing 50 modified-release tablets.

Carton containing 1 bottle of 50 modified-release tablets.

Carton containing 2 bottles of 50 modified-release tablets (100 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

Plenadren 5 mg modified-release tablets
EU/1/11/715/001
EU/1/11/715/003

Plenadren 20 mg modified-release tablets
EU/1/11/715/002
EU/1/11/715/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd November 2011
Date of latest renewal: 8th August 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

Shire Pharmaceuticals Ireland Limited
Block 2 & 3 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Plenadren 5 mg modified-release tablets
hydrocortisone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release tablet contains hydrocortisone 5 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release tablet

50 modified-release tablets
100 modified-release tablets (2x50)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow the tablets whole. Do not divide, crush or chew tablets.

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/715/001 50 modified-release tablets
EU/1/11/715/003 100 (2x50) modified-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plenadren 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Plenadren 5 mg modified-release tablets
hydrocortisone
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 modified-release tablets

6. OTHER

Takeda

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Plenadren 20 mg modified-release tablets
hydrocortisone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified-release tablet contains hydrocortisone 20 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Modified-release tablet

50 modified-release tablets
100 modified-release tablets (2x50)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow the tablets whole. Do not divide, crush or chew tablets.

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/715/002 50 modified-release tablets
EU/1/11/715/006 100 (2x50) modified-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plenadren 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Plenadren 20 mg modified-release tablets
hydrocortisone
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 modified-release tablets

6. OTHER

Takeda

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Plenadren 5 mg modified-release tablets
Plenadren 20 mg modified-release tablets
hydrocortisone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Plenadren is and what it is used for
2. What you need to know before you take Plenadren
3. How to take Plenadren
4. Possible side effects
5. How to store Plenadren
6. Contents of the pack and other information

1. What Plenadren is and what it is used for

Plenadren contains a substance called hydrocortisone (sometimes called cortisol). Hydrocortisone is a glucocorticoid. It belongs to a group of medicines called corticosteroids. Glucocorticoids occur naturally in the body, and help to maintain your general health and well-being.

Plenadren is used in adults to treat a condition known as adrenal insufficiency, or cortisol deficiency. Adrenal insufficiency occurs when your adrenal glands (just above your kidneys) do not produce enough of the hormone cortisol. Patients suffering from long-term (chronic) adrenal insufficiency need a replacement therapy to survive.

Plenadren replaces the natural cortisol that is missing in adrenal insufficiency. The medicine delivers hydrocortisone to your body throughout the day. The cortisol levels in your blood increase rapidly to a maximum level, about 1 hour after taking the tablet in the morning, and then gradually decrease 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.

2. What you need to know before you take Plenadren

Do not take Plenadren
- if you are allergic to hydrocortisone or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Plenadren
- when you have a condition that makes you unable to take this medicine or when the medicine is not absorbed properly from your stomach. This may happen when you have stomach problems involving vomiting and/or diarrhoea. In these situations you should seek immediate medical care in order to receive treatment with injections of hydrocortisone and extra fluid administration.

- if you have short-term or temporary illness such as infections, fever or situations causing a great amount of physical stress, such as surgery: your dose of hydrocortisone must be temporarily increased. Ask your doctor promptly for information on how you should handle these situations. If you are to have surgery, tell your doctor/dentist before the surgery that you are taking this medicine.
- if for any other reason your general health is declining although you take your medicine as prescribed; seek immediate medical care.
- if you have pheochromocytoma (a rare tumour of the adrenal glands).
- if your thyroid gland is not working normally tell your doctor since your dose of Plenadren may need to be adjusted.

Children and adolescents
Plenadren is not recommended for use in children and adolescents under 18 years old as it has not been studied in these patients.

Other medicines and Plenadren
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. During long term treatment with medicines treating infections (antibiotics) the dose of Plenadren may need adjustment by your doctor. If used with mifepristone, a treatment used to end a pregnancy, the effect of Plenadren may be reduced.

In addition, tell your doctor or pharmacist if you are using any of the following medicines, as the dose of Plenadren may need to be changed:

- Phenytoin, carbamazepine and barbiturates - used to treat epilepsy
- Rifampicin or rifabutin - used to treat tuberculosis
- Ritonavir, efavirenz and nevirapine – used to treat HIV infection
- St. John's wort - used to treat depression and other conditions
- Ketoconazole, itraconazole, posaconazole and voriconazole - used to treat fungal infections
- Erythromycin, telithromycin and clarithromycin - used to treat bacterial infections

Plenadren with food and drink
Do not take this medicine with grapefruit juice as the juice will conflict with the action of this medicine.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is important that you continue treatment with Plenadren during pregnancy. Treatment in pregnant women with adrenal insufficiency is unlikely to cause any harmful effects on the mother and/or the baby. You should tell your doctor if you become pregnant as the dose of Plenadren may have to be adjusted.

You can breast-feed during Plenadren treatment. Hydrocortisone is excreted in breast milk. Doses of hydrocortisone used for replacement therapy are unlikely to have any effect on the child. However, talk to your doctor if you plan to breast-feed your baby.

Fertility in women with adrenal insufficiency or cortisol deficiency may be reduced. There is no indication that Plenadren, in doses used for replacement therapy, will have an effect on fertility.

Driving and using machines
This medicine may have minor influence on your ability to drive and use machines. Extreme tiredness and episodes of short-lasting dizziness (vertigo) have been reported. Poorly treated or untreated adrenal insufficiency reduces your ability to concentrate and will affect your ability to drive and use machines. It is therefore important to take this medicine as directed by your doctor when driving or

using machines. If you are affected do not drive or use machines, until you have discussed the issue with your doctor.

3. How to take Plenadren

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The dose is specific for you and is decided by your doctor.

- When you wake up in the morning swallow Plenadren tablets whole with a glass of water at least 30 minutes before your breakfast, preferable between 6.00 am and 8.00 am in the morning.
- You should preferably be in an upright position.
- Do not divide, crush or chew the tablets. These tablets deliver hydrocortisone to your body throughout the day. If divided, crushed or chewed this may prevent the hydrocortisone dose in the tablet to cover the whole day, as it should.

The need for additional doses of Plenadren

During short-term or temporary illnesses such as infection, fever, or physical stress such as surgery you will need more hydrocortisone since the body cannot produce the additional amount of cortisol required in these situations. The dose must therefore be increased temporarily and your doctor may advise you to use other hydrocortisone tablets instead of, or in addition to Plenadren. Please discuss this with your doctor and follow the instructions on how to act in these situations.

The daily dose of Plenadren may have to be doubled or tripled in milder conditions such as a mild infection or stress. You should then take the second dose of this medicine 6 to 10 hours after the morning dose. If it is not enough to double the daily dose, you should take a third dose 6 to 10 hours after the second dose (6-10 hour intervals between doses). When your illness is over, return to your normal maintenance dose of this medicine.

The following signs and symptoms may suggest that you need to take additional doses of Plenadren or other forms of hydrocortisone: fatigue, weight loss, stomach discomfort, feeling light headed when you change from sitting to standing or dizziness when standing, darkening of your skin particularly skin creases and exposed areas. Contact your doctor promptly for advice if you notice any of these.

However, **seek immediate medical help** if you notice any of the following: severe weakness, fainting, abdominal pain, nausea, vomiting, back pain, confusion, reduced consciousness, delirium (very confused state).

If you take more Plenadren than you should

A too high dose of this medicine for more than a few days may be harmful to your health. Your blood pressure may increase, you may gain extra weight and your blood sugar may become too high. An increased dose is necessary occasionally in order for the body to cope with increased stress such as fever. If extra doses are needed frequently and regularly, you should contact your doctor for re-evaluation of your maintenance dose.

If you forget to take Plenadren

If you have forgotten to take your tablet in the morning, take it as soon as possible thereafter. Do not take a double dose to make up for a forgotten dose. If you experience any signs or symptoms listed in the section “The need for additional doses of Plenadren”, contact your doctor immediately.

If you stop taking Plenadren

Stopping Plenadren may be life threatening. It is therefore important to continue taking this medicine as prescribed by your doctor. Do not stop taking it without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you are changing treatment from other hydrocortisone tablets to Plenadren you may experience side effects during the first weeks. These side effects can be: stomach pain, feeling sick and tiredness. They will normally disappear with time, if not contact your doctor.

Side effects of this medicine are:

Very common (may affect more than 1 in 10 people)
- Dizziness
- Headache
- Diarrhoea
- Tiredness

Common (may affect up to 1 in 10 people)
- Stomach pain/heartburn, feeling sick or nauseated
- Pain in the joints
- Rash
- Itchiness

Additional side effects have been reported for other hydrocortisone medicines. These medicines have also been given for other indications than adrenal insufficiency replacement therapy, often in higher doses. Frequencies of these possible side effects are not known (frequency cannot be estimated from the available data). Talk to your doctor if you experience any of these side effects:

- More prone to infection
- Diabetes or problems with blood sugar levels (shown in blood tests)
- Salt and water retention causing swelling and raised blood pressure (shown on medical examination) and low potassium level in the blood
- Mood changes such as feelings of overexcitement or losing touch with reality
- Difficulty sleeping
- Raised pressure in the eye (glaucoma), clouding of the lens in the eye (cataract)
- Heartburn, aggravation of any existing stomach ulcer
- Weakening of the bones - this may cause bone fractures
- Stretch marks, bruising, acne-like rash, excessive growth of facial hair, slow wound healing.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Plenadren

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Plenadren contains

- The active substance is hydrocortisone.
  Plenadren 5 mg: Each modified-release tablet contains 5 mg of hydrocortisone.
  Plenadren 20 mg: Each modified-release tablet contains 20 mg of hydrocortisone.

- The other ingredients are hypromellose, microcrystalline cellulose, pregelatinised starch (maize), colloidal anhydrous silica and magnesium stearate. The coating system is a mixture of macrogol (3350), polyvinyl alcohol, talc and titanium oxide (E171). The 5 mg tablets also contain red iron oxide (E172), yellow iron oxide (E172) and black iron oxide (E172).

What Plenadren looks like and contents of the pack
The modified-release tablets are round (diameter 8 mm) and convex.
Plenadren 5 mg: the tablets are pink.
Plenadren 20 mg: the tablets are white.

Plenadren comes in bottles with a screw cap containing 50 tablets.

Pack sizes:
Carton containing one bottle of 50 modified-release tablets.
Carton containing 2 bottles of 50 modified-release tablets (100 tablets).

Not all pack sizes may be available in your country.

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.