Part VI: Summary of the risk management plan

Summary of risk management plan for Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets (Hydrocortisone), in AT-RMS Hydrocortison Hualan 2,5 mg Tabletten, Hydrocortison Hualan 5 mg Tabletten, Hydrocortison Hualan 10 mg Tabletten, Hydrocortison Hualan 15 mg Tabletten, Hydrocortison Hualan 20 mg Tabletten

This is a summary of the risk management plan (RMP) for Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets. The RMP details important risks of Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets, how these risks can be minimised, and how more information will be obtained about Hydrocortisone Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets's risks and uncertainties (missing information).

Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets should be used.

Important new concerns or changes to the current ones will be included in updates of Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets´s RMP.

I. The medicine and what it is used for

Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets are indicated for use as replacement therapy in primary or secondary adrenocortical insufficiency, in prevention of an acute adrenocortical crisis, and pre-operatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve.

It contains hydrocortisone as the active substance and it is given orally.

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

Important risks of Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets, together with measures to minimise such risks and the proposed studies for learning more about Hydrocortisone Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets's 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 collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets 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 Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets. 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).

Summary of safety concerns	
Important identified risks	Steroid withdrawal syndrome
Important potential risks	Phaeochromocytoma crisis Cerebellar growth impairment Teratogenicity
Missing information	None

II.B Summary of important risks

Important identified risk information	
Steroid withdrawal syndrome	
Evidence for linking the risk to the medicine	This important identified risk has been included in the list of safety concerns based on the PSUSA outcome.
Risk factors and risk groups	Patients receiving significant steroid dose for longer period of time are at risk of developing steroid withdrawal syndrome (Iliopoulou et al., 2013, Margolin et al., 2007).
Risk minimisation measures	Routine risk minimisation measures: Listings in SmPC section 4.4, 4.8. Listings in PIL section 3. Prescription only medicine.

Important potential risk information	
Pheochromocytoma crisis	
Evidence for linking the risk to the medicine	This important potential risk has been included in the list of safety concerns based on the PSUSA outcome.
Risk factors and risk groups	In most patients, pheochromocytomas occur randomly for unknown reasons (sporadically). In approximately 35% of cases, pheochromocytomas may be inherited in an autosomal dominant pattern. Pheochromocytomas affect males and females in equal numbers and may affect individuals of any age. These tumors occur most often in individuals between 30 and 50 years of age (NORD – Pheochromocytoma). The pheochromocytoma crisis can be precipitated by commonly used medications including corticosteroids, metoclopramide, and anesthetic agents like ketamine and halothane, in patients with pheochromocytoma (Chandrashekar et al, 2021).
Risk minimisation measures	Prescription only medicine.

Important potential risk information	
Cerebellar growth impairment	
Evidence for linking the risk to the medicine	This important potential risk has been included in the list of safety concerns based on the PSUSA outcome.
Risk factors and risk groups	Prematurely born babies treated with glucocorticoids for various reasons (e.g. to help with maintaining a normal blood pressure or to shorten the period of time they need help with breathing using a breathing tube).
Risk minimisation measures	Prescription only medicine.

Important potential risk information	
Teratogenicity	
Evidence for linking the risk to the medicine	This important potential risk has been included in the list of safety concerns based on the PSUSA outcome.
Risk factors and risk groups	Teratogenicity is the ability to cause defects in developing fetus. Multiple studies in the past investigated the effects if hydrocortisone on the pregnancy outcomes in animals. The potential of hydrocortisone, prednisolone and dexamethasone to produce cleft palate in pregnant mice was observed in a study (Pinsky et al, 1965), with highest Dexamethasone having the highest teratogenic potential. In rabbits, it was

	observed that a subcutaneous dose of hydrocortisone could induce polycystic kidney disease in the fetus (Crocker et al, 1991). Glucocorticoids, applied ocularly to a pregnant mice, significantly increased the incidence of cleft palate in fetuses (Ballard et al, 1977). Using data from National Birth Defect Prevention Study (NBDPS) (Carmichael et al, 2007), an association was found between maternal corticosteroid use and cleft lip with or without palate ([OR] 1.7; [CI] 1.1-2.6). Although a study (Skuladottir, 2014) using more recent NBDPS data showed no association between maternal corticosteroid use and cleft lip and palate in the offspring.
Risk minimisation measures	Routine risk minimisation measures Listing in the SmPC section 5.3. Prescription only medicine.

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 Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets.

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

There are no studies required for Hydrocortisone 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg Tablets.