Part VI: Summary of the risk management plan

Summary of risk management plan for Efmody® (Hydrocortisone modified-release capsules)

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

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

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

I. The medicine and what it is used for

Efmody is authorised for replacement therapy for congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults. It contains hydrocortisone as the active substance and it is given by mouth.

Further information about the evaluation of Efmody's benefits can be found in Efmody's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/efmody* .

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

Important risks of Efmody, together with measures to minimise such 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 periodic risk benefit evaluation report (PBRER) 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 Efmody 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 Efmody. 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	None
Important potential risks	Growth retardation (in off-label paediatric use) Accelerated sexual maturation (in off-label paediatric use)
Missing information	None

II.B Summary of important risks

Important potential risk: Growth retardation (in off-label paediatric use)	
Evidence for linking the risk to the medicine	Growth retardation has been well recognised in children on chronic steroids and is dose-related. The situation in CAH can be complicated by the underlying disease and/or comorbidities. In CAH growth can be accelerated by androgen excess, however this is accompanied by bone age acceleration leading to precocious puberty, early fusion of epiphyses and compromised final height. Conversely, overdose of steroids will suppress this androgen effect but cause growth retardation. Owing to difficulties in interpreting historical data with higher dose regimens of replacement steroids, absence of untreated cohort data due to the lethal nature of disease, and interaction between growth, disease and steroids in CAH, it is difficult to determine the true extent of this problem in the present day.
Risk factors and risk groups	Cohort analysis has highlighted two periods during childhood and adolescence during which maintenance of normal growth velocity is especially important for final

	height; during the first 6 months of life and during puberty (**Error! Reference source not found.**). Retrospective analysis of the dose-dependence of growth retardation effects of glucocorticoids in CAH patients has shown that the lowest possible dose should be used.
Risk minimisation measures	Routine risk minimisation: Text in SmPC section 4.2, 4.4, 4.8 Text in PIL section 2
Important potential risk: Accelerated sexual maturation (in off-label paediatric use)	
Evidence for linking the risk to the medicine	Risk of accelerated sexual maturation in children with CAH is well known among endocrinologists and is caused by excess adrenal androgens when the condition is untreated or poorly controlled. Optimised glucocorticoid replacement therapy in CAH limits excess adrenal androgen production, thereby normalising sexual maturation. It is difficult to determine the frequency of accelerated sexual maturation in CAH patients treated with hydrocortisone; some reports indicate onset of puberty is more or less normal and other studies show earlier onset of aspects of pseudo-puberty such as pubarche and thelarche.
Risk factors and risk groups	There is no consistent evidence that patient sex or clinical severity in classic CAH is a specific risk factor for accelerated sexual maturation. Published reports conclude that a key risk factor for accelerated sexual maturation may be glucocorticoid undertreatment leading to inadequate androgen control.
Risk minimisation measures	Routine risk minimisation: Text in SmPC section 4.2, 4.4, 4.8 Text in PIL section 2

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 Efmody.

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

N/A