



Public Assessment Report

Decentralised Procedure

**Hydrocortisone 100mg, powder for solution for
injection/infusion**

(hydrocortisone sodium succinate)

Procedure No: UK/H/6296/001/DC

UK Licence No: PL 41947/0029

ELC GROUP s.r.o.

LAY SUMMARY

Hydrocortisone 100mg, powder for solution for injection/infusion

This is a summary of the Public Assessment Report (PAR) for Hydrocortisone 100mg, powder for solution for injection/infusion (PL 41947/0029; UK/H/6296/001/DC). It explains how Hydrocortisone 100mg, powder for solution for injection/infusion was assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Hydrocortisone 100mg, powder for solution for injection/infusion.

The product will be referred to as Hydrocortisone throughout the remainder of this public assessment report (PAR).

For practical information about using Hydrocortisone patients should read the package leaflet or contact their doctor or pharmacist.

What is Hydrocortisone and what is it used for?

Hydrocortisone is a 'generic medicine'. This means that Hydrocortisone is similar to a 'reference medicine' already authorised in the European Union (EU) called Solu-Cortef 100 mg (Pfizer Limited, UK).

Hydrocortisone is used to treat **shock** following surgery, injuries, hypersensitivity (**anaphylactic**) reactions or other stressful conditions. These include inflammatory or allergic conditions affecting the:

- **bowel and gut** e.g. Crohn's disease (inflammation of the gut) or ulcerative colitis (inflammation of the lower bowel)
- **lungs** e.g. bronchial asthma or inflammation caused by breathing in (aspirating) vomit or stomach contents
- **skin** e.g. Stevens-Johnson syndrome (an autoimmune disorder in which an immune system causes the skin to blister and peel), or systemic lupus erythematosus (lupus)

How does Hydrocortisone work?

This medicine contains the active ingredient hydrocortisone as hydrocortisone sodium succinate.

Hydrocortisone belongs to a group of medicines called corticosteroids or steroids. Corticosteroids are produced naturally in the body and are important for many body functions.

Boosting the body with extra corticosteroid such as Hydrocortisone can help when injected by a doctor or nurse to treat the conditions described above.

How is Hydrocortisone used?

Steroid Cards

The patient should remember to always carry a Steroid Treatment Card. The patient should make sure their doctor or pharmacist has filled out the details of their medicine, including the dose and how long they will require steroid treatment.

The patient should show their steroid card to **anyone** who gives them any medical treatment (such as a doctor, nurse or dentist) while they are receiving this medicine, and for 3 months after their last injection.

If the patient is admitted to hospital for any reason, they should always tell their doctor or nurse that they are being treated with this medicine. The patient can also wear a medic-alert bracelet or pendant to let medical staff know that they are treated with a steroid if they have an accident or become unconscious.

The pharmaceutical form of this medicine is a powder for solution for injection/infusion. The route of administration of this medicine is either into a vein (intravenous) or into a muscle (intramuscular).

Hydrocortisone will be given as an injection to the patient by a doctor or a nurse.

The patient's doctor will decide on the site of injection, how much of the medicine and how many injections they will receive depending on the condition being treated and its severity. The doctor will inject the patient with the lowest dose for the shortest possible time to get effective relief of their symptoms.

Adults

Usually the first dose is given into a vein, especially in an emergency.

It will be given slowly over a period of between 1 – 10 minutes. Depending on the patient's condition a repeat dose may be injected at intervals of between 2 to 6 hours. Large doses should normally be used for only two to three days. The medicine is first dissolved in sterile water for injections. If the medicine is to be given by infusion (using a pump or drip) it is then also mixed with another suitable fluid. No other medicines should be mixed with this medicine.

Elderly patients

Treatment will normally be the same as for younger adults. However, the patient's doctor may want to see them more frequently to check how they are getting on with this medicine.

Use in children and adolescents

Corticosteroids can affect growth in children so the doctor will prescribe the lowest dose (should not be less than 25 mg a day) that will be effective for a child.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Hydrocortisone have been shown in studies?

No additional clinical studies were needed as Hydrocortisone is a generic medicine that after reconstitution is an aqueous solution that is given by injection or infusion and contains the same active as the reference medicine Solu-Cortef 100 mg (Pfizer Limited, UK).

What are the possible side effects of Hydrocortisone

Because Hydrocortisone is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Hydrocortisone, see section 4 of the package leaflet available on the MHRA website.

Why was Hydrocortisone approved?

It was concluded that, in accordance with EU requirements, Hydrocortisone has been shown to be comparable to Solu-Cortef 100 mg (Pfizer Limited, UK). Therefore, the MHRA decided that, as for Solu-Cortef 100 mg (Pfizer Limited, UK), the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Hydrocortisone?

A risk management plan (RMP) has been developed to ensure that Hydrocortisone is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Hydrocortisone including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Hydrocortisone

Malta and the UK agreed to grant a Marketing Authorisation for Hydrocortisone on 08 November 2017. A Marketing Authorisation was granted in the UK on 28 November 2017.

The full PAR for Hydrocortisone follows this summary.

For more information about treatment with Hydrocortisone, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Hydrocortisone (PL 41947/0029; UK/H/6296/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1. *Collagen diseases*
Systemic lupus erythematosus
2. *Dermatological diseases*
Severe erythema multiforme (Stevens-Johnson syndrome)
3. *Allergic states*
Bronchial asthma, anaphylactic reactions
4. *Gastro-intestinal diseases*
Ulcerative colitis, Crohn's disease
5. *Respiratory diseases*
Aspiration of gastric contents

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS). The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Solu-Cortef 100 mg which was first granted to Pharmacia Limited on 18 May 1990 (PL 00032/5019R) and subsequently underwent a change of ownership procedure to the current marketing authorisation holder Pfizer Limited on 18 February 2015 (PL 00057/1050).

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. It is a glucocorticosteroid. Used in pharmacological doses, its actions suppress the clinical manifestations of disease in a wide range of disorders.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference product are aqueous intravenous solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 08 November 2017. After a subsequent national phase, a licence was granted in the UK on 28 November 2017.

II QUALITY ASPECTS

II.1 Introduction

Each vial contains hydrocortisone sodium succinate 133.7 mg equivalent to hydrocortisone 100.0 mg.

The finished product is packed into type III colourless glass vials closed by a grey radiosterilised bromobutyl rubber closure and capped with an aluminium flip cap with blue plastic disk and is available in a pack size of one box containing 10 vials.

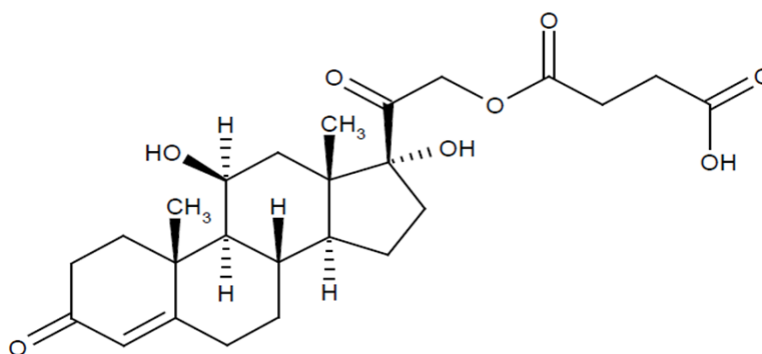
The medicinal product contains sodium hydrogen phosphate buffer as the sole pharmaceutical excipient. Appropriate justification for the inclusion of sodium hydrogen phosphate buffer has been provided.

II.2. Drug Substance

INN: Hydrocortisone hydrogen succinate

Chemical name: $11\beta,17\alpha$ -dihydroxypregn-4-ene-3,20-dione-21-succinate

Structural formula:



Molecular formula: $C_{25}H_{34}O_8$

Molecular weight: 462.5 Da

Appearance: White or yellowish powder, humid

Solubility: Practically insoluble in water, freely soluble in acetone and in ethanol. It dissolves in dilute solutions of alkali carbonates and alkali hydroxides.

Hydrocortisone hydrogen succinate is the subject of a European Pharmacopeia monograph.

All aspects of the manufacture and control of the active substance, hydrocortisone hydrogen succinate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data that comply with the proposed specification are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious powder for solution for injection/infusion containing hydrocortisone sodium succinate 133.7 mg equivalent to hydrocortisone 100.0 mg per vial that is comparable to the originator product Solu-Cortef 100 mg (Pfizer Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

This product contains no materials of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened vial with the storage conditions 'Store in the original package in order to protect from light.'

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C and 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The Applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Hydrocortisone is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

According to the regulatory requirements of CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted any.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of Hydrocortisone.

Based on the data provided, Hydrocortisone can be considered a generic of Solu-Cortef 100 mg (Pfizer Limited, UK).

IV.2 Pharmacokinetics

In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as a parenteral aqueous solution containing the same qualitative and quantitative composition in terms of active substance and excipients and is of the same pharmaceutical form as the currently approved product. No bioequivalence study has been submitted with these applications and none is required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating Hydrocortisone.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Use in patients hypersensitive to hydrocortisone and any of the ingredients • Use in patients with systemic infections and increased susceptibility to infections • Concomitant use with live vaccines and use in patients vaccinated with live vaccines • Adrenal cortical atrophy with prolonged use • Use in patients with cardiac disorders (hypertension, myocardial infarction, and congestive heart failure) • Use in patients with endocrine disorders (diabetes, or with a family history of diabetes; hypothyroidism; and osteoporosis) • Use in patients with glaucoma (or family history of glaucoma) • Use in patients with previous corticosteroid induced myopathy • Use in patients with peptic ulcers • Withdrawal symptoms • Severe psychiatric adverse reactions • Growth retardation in infancy, childhood and adolescence • Use in the elderly • Use in patients with liver failure • Concomitant use of medicines which enhance or inhibit the metabolism of corticosteroids • Concomitant use with hypoglycaemic drugs (including insulin), antihypertensives and diuretics • Concomitant use with coumarin anticoagulants • Concomitant use of salicylates or nonsteroidal anti-inflammatory drugs (NSAIDs) with corticosteroids • Hypokalaemia and concomitant use with potassium depleting medicines
Important potential risks	<ul style="list-style-type: none"> • Use during pregnancy and lactation
Missing information	None

Routine pharmacovigilance and risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

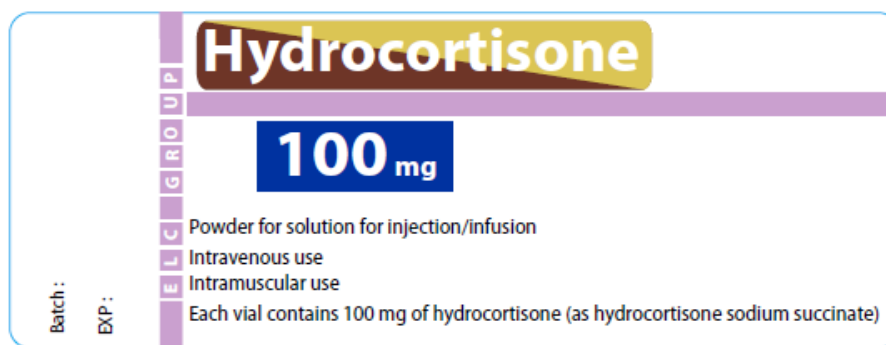
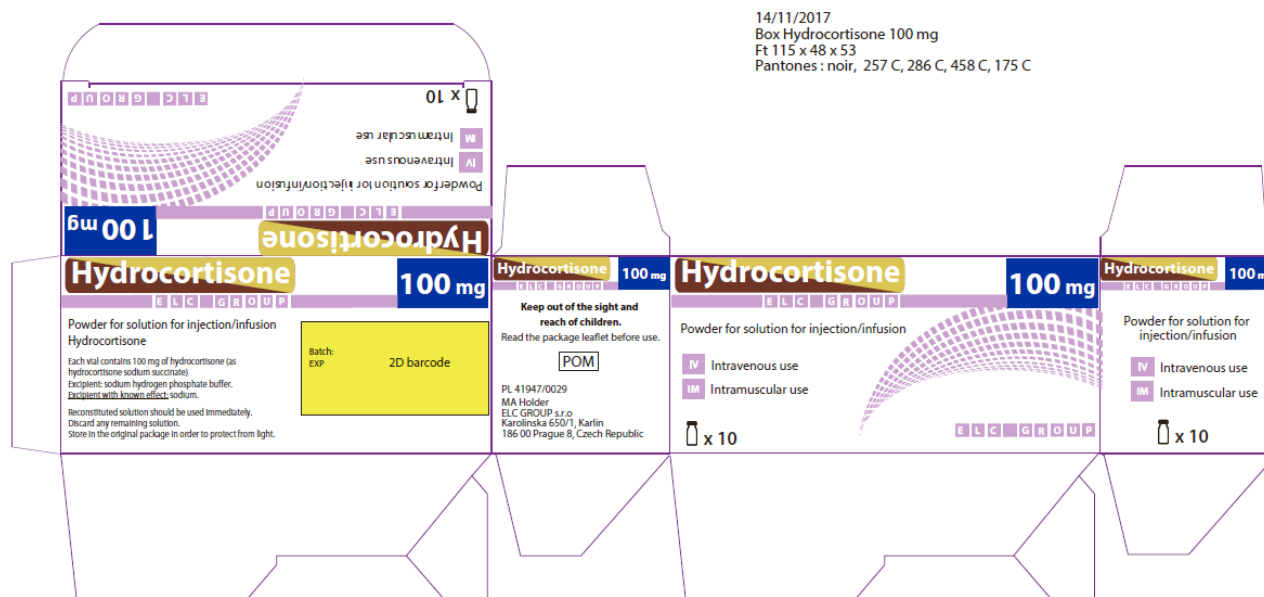
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with hydrocortisone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:



Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome