LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Isicort
(dexamethasone)

SE/H/2183/01-03/MR

This module reflects the scientific discussion for the approval of Isicort. The procedure was finalised on 2020-09-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AcuCort AB has applied for a marketing authorisation for Isicort, 4 mg, 6 mg, 8 mg, orodispersible film. The active substance is 2examethasone (a synthetic glucocorticoid with anti-inflammatory and immunosuppressive effect).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well known.

III.2 Pharmacology

No pharmacology studies have been performed by the applicant.

III.3 Pharmacokinetics

In the combined pharmacokinetic and local tolerance study provided by the applicant the effect of the eucalyptol and menthol levels on the transmucosal absorption rate of dexamethasone and local tolerance were assessed in hamsters treated with the development formulation Dexa ODF 8 mg (one piece of 1 cm^2, corresponding to 1.1 mg). The pharmacokinetic analyses revealed no dexamethasone in plasma of animals treated with effect of eucalyptol and menthol levels (at 7.2%) on the transmucosal absorption rate and no treatment-related oral irritation was observed after treatment with formulation including 0, 7.2 or 21.6% of eucalyptol and menthol. It can therefore be considered that no mucosal absorption or oral irritation would occur when given the current formulation, an orodispersible film.

III.4 Toxicology

No toxicology studies have been performed except for local tolerance (see pharmacokinetics above).

III.5 Ecotoxicity/environmental risk assessment

No ERA has been submitted which is considered acceptable since Isicort will be used as an alternative to currently available medicinal products containing dexamethasone and it is therefore not anticipated that there will be an additional use of products containing dexamethasone compared to the present usage, and thereby not judged to be an additional risk to the environment from this medicinal product.

IV. CLINICAL ASPECTS

IV.1 Introduction

Isicort is an orodispersible film containing dexamethasone developed to offer a product that is convenient to use.

IV.2 Pharmacokinetics

To support the marketing authorisation application, the applicant has conducted one bioequivalence study (AcuCort002) comparing Isicort with the reference product Fortecortin.

The applicant also submitted one bioavailability study with a preliminary formulation (AcuCort001) and two bioequivalence studies (AcuCort003 and AcuCort004) performed with a reference product registered in the US and these two studies were conducted to support the US development program.

Pharmacokinetic properties of the active substance

Absorption: Dexamethasone is rapidly and almost completely absorbed in the stomach and small intestine after oral administration. Bioavailability after oral administration is 80% to 90%.
Peak plasma concentration is reached 1-2 hours after administration.

Elimination: The plasma half-life of dexamethasone observed in the submitted studies AcuCort001 to AcuCort003, is in line with the plasma half-life of approximately 3 – 4.5 hours reported in literature.

Study AcuCort002

Methods

This was a single-dose, two-way crossover study conducted in 30 healthy volunteers (28 subjects completed), comparing Isicort, 1 x 8 mg, orodispersible film with Fortecortin, 2 x 4 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of dexamethasone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 13 October 2018 and 27 October 2018.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dexamethasone, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**421.75 ± 110.43**	**72.59 ± 19.09**	**1.25 (0.50-2.50)**
Reference	**408.33 ± 99.72**	**66.28 ± 17.92**	**1.13 (0.50-8.00)**
***Ratio (90% CI)**	**102.59 (98.38-106.98)**	**109.38 (99.41-120.34)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 4 mg and 6 mg.

IV.3 Pharmacodynamics

Dexamethasone is a synthetic long-acting glucocorticoid with anti-inflammatory, antipyretic and immunosuppressive properties and no mineralocorticoid properties.

The pharmacodynamic properties of dexamethasone are well known. As dexamethasone is a widely used, well-known active substance, no further studies are required, and the applicant provides none. The pharmacodynamic data presented through a literature review is considered to be appropriate.

IV.4 Clinical efficacy

Dexamethasone was introduced in 1952 and consequently has been used clinically for an extensive period of time.

The reference product is Fortecortin tablets, approved in the following indications:

Conditions requiring anti-inflammatory and immunosuppressant treatment including:

- Treatment of cerebral oedema secondary to brain tumours, neurosurgery, brain abscesses
- Treatment of acute severe asthma
- Initial treatment of severe acute skin diseases
- Initial treatment of autoimmune diseases
- Treatment of active rheumatoid arthritis
- Prophylaxis and treatment of nausea and vomiting induced by cytostatic agents as part of antiemetic regimens

In addition to the above indications, two additional indications have been added:

- Allergic reactions including acute allergic reactions
- Croup

No new clinical studies have been provided. An overview of the literature supporting the indications were provided. In the following, data supporting the use of dexamethasone in the newly added indications is summarised.

Allergic reactions including acute allergic reactions
Corticosteroids have an anti-inflammatory effect in allergy and have been used for treatment of allergic diseases since 1949, when cortisone was introduced. Corticosteroids block different inflammatory pathways that are abnormally activated in allergic diseases, thereby resulting in a clinical effect. Although likely related to the late (second) phase allergic reaction, the exact mechanism of action is not known.

Oral administration of dexamethasone is as effective as i.v. administration and is preferred because it is quicker and less invasive. Dexamethasone does have a strong anti-inflammatory effect and can be used in management of allergic reactions and as an adjuvant in the treatment of acute allergic reactions including anaphylaxis. Treatment guidelines indicate different ranges of dexamethasone doses. Individualized doses are recommended for other registered dexamethasone products. Overall, for children 0.15-0.6 mg/kg bodyweight is recommended with a maximum single dose of 12 mg, for adults a starting dose of 4 to 10 mg is recommended with a maximum single dose of 12 mg.

Dexamethasone has been shown to be an effective treatment of allergic reactions of cytostatic-induced allergic reactions. A meta-analysis showed that oral dexamethasone prophylactic treatment is superior to intravenous dexamethasone prophylactic treatment of paclitaxel-induced allergic reactions.

The use of dexamethasone alone or with other drugs is in line with local Swedish treatment guidelines for the treatment of allergy and acute allergic reactions. Of note, for acute allergic reactions, the effect of corticosteroids is only evident a few hours after initiation of treatment.

Acute allergic reactions, such as anaphylaxis, are medical emergencies and thus no randomized controlled clinical trials have been identified in this emergency condition. Therefore, current guidelines on the use of corticosteroids, such as dexamethasone, are mostly based on data from observational studies, animal and laboratory studies. Some publications report resistance of acute allergic reactions, including anaphylaxis, to steroids. Even though dexamethasone may not provide instant relief of the acute allergic reactions, it may be relevant as one of a combination of drugs used to treat acute allergic reactions.

Although it is difficult to study the effect of dexamethasone in controlled clinical trials due to the acute nature of acute allergic reactions, there are some cases in literature describing the use of dexamethasone as rescue medicine. In these cases, dexamethasone is used in combination with other agents, such as epinephrine.

Across the EU medicinal products containing dexamethasone as the active substance are registered for the use in (acute) allergic reactions including anaphylaxis.

Croup
The exact mechanism of the administration of steroids in croup is not fully understood, but it is known that glucocorticoids have vasoconstrictive effects that may contribute to their clinical actions by resulting in reduced airway oedema, less micro-vascular leakage, and reduced airway mucus production. When used as croup treatment, glucocorticoids act on the subglottic oedema, thereby reducing the inflammation in the airway obstruction as quickly as one hour after administration. A decrease in these inflammatory properties results into a reduction in the difficulty of breathing for the child.

According to the Applicant, dexamethasone is the treatment of choice since benefits can be observed in croup patients with any severity. Dexamethasone can be given orally or intramuscularly, both having superior efficacy to placebo, but in most paediatric emergency departments oral dosage is the preferred mode of administration. The biological half-life of dexamethasone is around 36-54 hours, approximately double of that of other corticosteroids like prednisolone; therefore, the administration of a single dose of dexamethasone is quite effective.

- *Review studies*

A meta-analysis of 24 randomized controlled trials examining the effectiveness of glucocorticoid treatment in children with croup was performed. The analysis included studies in patients with croup, for which an intervention with glucocorticoid had to have been compared with either placebo or any other active treatment. Treatment with dexamethasone, budesonide, and prednisolone was evaluated. It was concluded that glucocorticoids were significant effective at improving croup severity score at 6 hours and at 12 hours, but was not significant at 24 hours. The number of adrenaline treatments needed in children could be reduced more greatly when treated with dexamethasone than with budesonide.

Another review concluded that there is clear evidence that corticosteroids are beneficial to children with symptoms of croup with different severities i.e. mild to severe. The publication advices 0.6 mg/kg oral dexamethasone during mild to moderate croup, for patients suffering from severe croup 0.6 mg/kg oral dexamethasone in combination with nebulized epinephrine is recommended along with blow-by oxygen if needed.

- *Clinical studies*

A trial was carried out among 80 children (aged 5 to 158 months) to compare the efficacy of oral dexamethasone and inhaled budesonide in children hospitalized with croup. Either 2 mg of nebulized budesonide, dexamethasone syrup (0.6 mg/kg) or a placebo was administered. For the dexamethasone and budesonide treated patients the median duration of hospitalization was reduced compared to those who received placebo (to 12 and 13 hours respectively compared to 20 hours for placebo). Also, the median time to a croup score of ≤1 was reduced to 2 and 3 hours, respectively, compared to 8 hours for placebo. After 1 hour the croup scores where significantly lower for both steroid groups than for the placebo group. The study concluded that both oral dexamethasone and inhaled budesonide are effective in reducing symptoms and duration of hospitalization in hospitalized children with croup. An additional study showed that oral dexamethasone is also effective in patients with mild croup, reducing need to return to medical care (see table below).

Another publication presents a randomized trial of 120 children, all hospitalized with croup, aged > 6 to 160 months, who were divided in two sequential double-blind, randomized trials. In Trial A 60 children received either 0.6 or 0.3 mg/kg dexamethasone syrup; in Trial B 60 children received either 0.3 or 0.15 mg/ kg dexamethasone syrup. In both trials, croup scores did not differ following treatment, although scores were significantly lower compared to initial scores. Also, no differences were seen regarding hospitalization time, use of adrenaline, readmission to hospital with croup following discharge from hospital. The study concluded that oral dexamethasone in the treatment of croup is effective, and the use of 0.15, 0.3 or 0.6 mg/kg results in similar relieve of symptoms and similar duration of hospitalization in children with croup.

A retrospective analysis of 188 medical records of paediatric patients (mean age of the 33.0±17.2 months) who were brought via the emergency medical services to the emergency department showed that pre-hospital administration of dexamethasone results in less epinephrine use and may reflect dexamethasone's positive influence on the severity and short-term persistence of croup symptoms.

Table 2 provides an overview of double-blind randomized trials assessing the use of oral dexamethasone.

Table 2: Overview of Clinical Trials conducted with Dexamethasone in croup patients

Patient Group, number (n) and Age	**Study Design** **Dosing**	**Outcomes**	**Key Results**
Children (n=100) Aged 4-122 months with mild croup, presented to the emergency	Double-blind randomized, placebo-controlled trial Dosing: single oral dose of	Return to medical care with ongoing croup	Eight children (all from the placebo group) returned to medical care with ongoing croup, one being admitted.

department but not admitted to hospital	dexamethasone 0.15 mg/kg or placebo		Oral dexamethasone in a dose of 0.15mg/kg is effective in reducing return to medical care with ongoing croup in children with mild croup.
Children (n=720) aged 12-58 months diagnosed with mild croup	Double-blind randomized trial Dosing: singe oral dose of either dexamethasone (0.6 mg per kg of body weight) or placebo	Primary outcome: return to a medical care provider for croup within seven days after treatment. Secondary outcome: presence of ongoing symptoms of croup on days 1, 2, and 3 after treatment.	Return to medical care was significantly lower in the dexamethasone group. In the dexamethasone group, there was quicker resolution of croup symptoms, less lost sleep, and less stress on the part of the parent
Children (n=72) aged 3 months to 9 year Diagnosed with croup, moderately severe respiratory distress	Double-blind randomized trial Sample size Dosing: Group A: oral dexamethasone (0.6 mg/kg), (n=36) Group B: oral dexamethasone (0.15 mg/kg), (n=36)	Reduction in croup score, hospitalization rate and admission and adrenaline usage	Oral dexamethasone in a dose of 0.15mg/kg is as effective as a dose of 0.6mg/kg in relieving symptoms of acute croup in children and results in similar reduction in croup score, adrenaline usage and overall hospital admission rate and duration-stay.
Children (n=133) aged 3 to 142 months with mild to moderate croup, presented to the emergency department	Double blind, randomized equivalence study. Dosing: single dose of oral 0.15 mg/kg dexamethasone or 1 mg/kg oral prednisolone.	Primary outcome: magnitude and rate of reduction in Westley croup score. Clinical observations at 30 minutes after administration of steroid; hourly for the next four hours and four hourly thereafter until discharge. Re-attendance at medical care within 7-10 days.	Five out of 68 (7%) children who had received dexamethasone returned for medical care *versus* 19/65 (29%) children who had received prednisolone. No significant difference between the three groups in magnitude or rate of Westley score reduction.
Children (n=99), aged 6 months to 6 years with mild or moderate croup, presented to the emergency department	Double blind, randomised trial. Dosing: Patients were randomised to one single oral dose of 1 mg/kg prednisolone, 0.15 mg/kg dexamethasone or	Primary outcome: magnitude and rate of reduction in Westley croup score, rate of return for medical care with ongoing croup, and further treatment with steroids in the	No significant difference in admission rates, duration of symptoms or attendances. No significant difference between treatment groups.

	0.6 mg/kg dexamethasone.	week following index presentation.	
Children (n=87) aged 1-8 years presenting to primary care offices with mild or moderate croup	Double blinded randomised comparison trial Dosing: Oral prednisolone 2 mg/kg per day for 3 days *versus* one oral dose of 0.6 mg/kg dexamethasone, followed by two days of one placebo dose each	Compare the effectiveness of prednisolone 2mg/kg for 3 days, with one dose of dexamethasone 0.6mg/kg	No differences in outcome between both treatments regarding additional health care for croup, duration of symptoms and QoL related matters such as nights with disturbed sleep for the parent and days with stress.

Across the EU dexamethasone is registered for the use in croup. Furthermore, local treatment guidelines do recommend the use of dexamethasone in mild to severe croup.

Taking literature, registered products and treatment guidelines into account; the recommended oral dexamethasone dose is 0.15 to 0.6 mg/kg in mild to moderate croup. In severe patients 0.6 mg/kg oral dexamethasone is recommended in combination with other treatment.

IV.5 Clinical safety

The safety profile of dexamethasone is well known. Most important risks of long-term use are adrenal suppression and induction of Cushing's syndrome. Long-term treatment with dexamethasone also increases the risk of opportunistic infections. Patients with diabetes mellitus are at greater risk because of the impaired carbohydrate tolerance. Other important safety concerns for dexamethasone products are osteoporosis, growth retardation in children, pheochromocytoma crisis and tumour lysis syndrome.

Dexamethasone is a corticosteroid with minimal mineralocorticoid effects, which lowers the risk of adrenal suppression. Most risks are dose and treatment duration dependent. The minimum effective dose should be maintained for as little time as possible. Dexamethasone dose should be reduced gradually to avoid withdrawal symptoms, which in turn can lead to serious events.

Dexamethasone has a peripheral catabolic action, promotes the gluco(neo)genesis, and has anti-inflammatory and immunosuppressive properties. Adverse events may result from these properties.

Specific adverse events
Isicort is a new dosage form of dexamethasone, an orodispersible film consisting of the drug substance in micronized form suspended in a polymeric matrix made of HPMC and with 5% of glycerol added. These excipients are well known and not expected to induce adverse reactions. No tolerance issues are expected when Isicort is used in human.

Orodispersible films are widely used and have proven acceptance and patient compliance with no risk of choking and are associated with better safety and efficacy in comparison with conventional dosage forms.

Use in specific populations
Use of this medicinal product during the growth phase is subject to strict management of the risk-benefit ratio (SmPC section 4.8 "Musculoskeletal and connective tissue disorders"). In a literature review, it was concluded that a short course of dexamethasone has limited side effects in children.

IV.6 Risk Management Plans

The Applicant has submitted a risk management plan, 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 to Isicort.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	Pheochromocytoma crisis Tumour lysis syndrome
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.3 signed 4 September 2020, is considered acceptable.

The 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 MPA;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

Pharmacokinetics
The bioequivalence study (AcuCort002) and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on literature data and the submitted studies indicates that the pharmacokinetics of dexamethasone is linear between 4 mg and 8 mg. Absence of studies with the additional strengths of 4 mg and 6 mg is acceptable from a pharmacokinetic point of view.

Based on the submitted bioequivalence study (AcuCort002), Isicort is considered bioequivalent with Fortecortin.

Pharmacodynamics

Dexamethasone is a synthetic long-acting glucocorticoid with anti-inflammatory, antipyretic and immunosuppressive properties and no mineralocorticoid properties. No further studies have been provided. The pharmacodynamic data presented through a literature review is considered to be appropriate.

Clinical efficacy

Isicort is submitted as a hybrid application, referring to the European reference product Fortecortin, approved in Spain. The drug product is formulated as an oral, immediate release orodispersible film, being an alternative for patients who have difficulties in swallowing tablets or capsules.

The following part of the indication, as well as the posology, is identical to the indication for the reference product Fortecortin, approved in Spain; for the treatment of conditions which require anti-inflammatory and immunosuppressant treatment, such as treatment of cerebral oedema secondary to brain tumours, neurosurgery, brain abscesses, treatment of acute severe asthma, initial treatment of severe acute skin disease, initial treatment of autoimmune diseases, treatment of active rheumatoid arthritis, prophylaxis and treatment of nausea and vomiting induced by cytostatic agents as part of antiemetic regimens'. These indications have been adequately supported by the literature data provided in the overview.

The proposed posology for the use of dexamethasone in severe asthma and rheumatoid arthritis has been brought in line with the recommendations in current treatment guidelines (GINA guideline, 2020; EULAR, 2020).

Literature data have also been provided which supports the use in the new indications, allergic reactions and croup, as well as the proposed posology. However, the currently available strengths limit the use in small children. Therefore, the use in small children has been limited to above 3 months of age and at least 7 kg of body weight. To further clarify the incremental steps based on the available strengths, a table has been included in section 4.2 of the SmPC under the heading "paediatric population".

Overall, the indication proposed for Isicort, listing the different conditions, is considered well supported by the literature data provided.

Clinical safety

The general safety profile of dexamethasone is well known due to the extensive use of the drug. No new safety signals arise from the bioavailability studies. Furthermore, no safety issues are expected from the new formulation as orodispersible film.

With this application, two new indications are applied for. However, available data in the literature support that no additional safety concerns arise from the use of dexamethasone in croup and allergic reactions, bearing in mind the severity of the conditions and the short-term use of the drug.

The safety information in the SmPC of Isicort is in line with the approved SmPC of the reference product as well as for other dexamethasone products.

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 Swedish.
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 hybrid product, Isicort, is found adequate. There are no objections to approval of Isicort from a non-clinical and clinical point of view. Bioequivalence between Isicort and the reference product Fortecortin has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Isicort, 4 mg, 6 mg, 8 mg, orodispersible film was approved in the national procedure on 2020-09-29.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2183/01-03/MR	Initial Mutual Recognition Procedure	Y	2021-12-21	Approval	N/A
N/A	To add as indication the treatment of COVID-19 patients requiring supplemental oxygen therapy	Yes	02Feb2021	Approval	Following the outcome of an Article 5(3) procedure, it was concluded that oral dexamethasone can be considered a treatment option for COVID-19 patients who require supplemental oxygen therapy. The RMP has been updated in order to reflect the new indication.

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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