EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report pursuant to Article 29(4) of Directive 2001/83/EC, as amended

Dexamethasone Alapis

INN of the active substance: Dexamethasone

Applicant: Alapis S.A.

Procedure no: EMEA/H/A-29/1308

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Alapis S.A submitted an application for decentralised procedure of Dexamethasone Alapis 0.4 mg/ml oral solution on 07 January 2010.

The application was submitted to the reference Member State (RMS): Malta and the concerned Member States (CMS): Greece, Cyprus, United Kingdom, Portugal, Belgium, Germany, Bulgaria and Romania.

The Decentralised procedure MT/H/0117/001/DC started on 26 March 2010.

On day 210, Germany major issues on safety and efficacy remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by Malta on 11 March 2011. The CMD(h) 60 day procedure was initiated on 28 March 2011.

Day 60 of the CMD(h) procedure was on 26 May 2011 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration under Article 29(4) of Directive 2001/83/EC, as amended, to the CHMP was made by Malta on 30 May 2011. Germany raised public health objections on the grounds that the submitted literature data mainly concerned tablets and that no bridging data had been provided to justify the extrapolation of the published data on the efficacy and safety of dexamethasone tablets to dexamethasone Alapis 0.4 mg/ml oral solution.

2. Scientific discussion during the referral procedure

2.1. Introduction

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties. It is used principally as an anti-inflammatory or immunosuppressant agent. The mechanism of action is mediated via activation of glucorticoid receptors that leads to increased or decreased transcription of a number of genes involved in the inflammatory process, particularly the repression of cytokine gene transcription and the direct interaction between the glucocorticoid receptor and other transcription factors activated in chronic inflammation. Because it has only minimal mineral corticoid properties, the drug is inadequate as a monotherapy for the management of adrenocortical insufficiency. Dexamethasone has a biological half life of 36 - 54 hours and therefore is suitable in conditions where continuous glucocorticoid action is required.

This active substance is considered to have a 'well-established use' within the European Community for at least 10 years, with recognised efficacy and an acceptable level of safety in the use in certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema and for diagnostic testing of adrenocortical hyperfunction.

The application for Dexamethasone Alapis has therefore been made in accordance with Article 10a of Directive 2001/83/EC, as amended.

The decentralised procedure was closed on day 210, with all the concerned member states agreeing with the RMS assessment report except one CMS, Germany, which raised a potential serious risk to

public health as it considered that the literature data on dexamethasone tablets that were submitted could not be extrapolated to dexamethasone oral solution without adequate bridging data and therefore the efficacy and safety of Dexamethasone Alapis could not be demonstrated in the application.

A referral was thus triggered at the CMD(h) and the Applicant was asked to provide detailed literature and critical assessment of the efficacy and safety of dexamethasone oral solution in the indications applied for. The Applicant specifically focussed its response on the concern raised about bridging data.

2.2. Critical evaluation

Literature data

From the literature submitted during the decentralised procedure, it was shown that dexamethasone has been widely used in clinical practice for a number of indications for more than 40 years. The EU Harmonised Birth Date of dexamethasone in the Community is 01.01.1952. The extent and the period over which dexamethasone is used in the Community is documented by the publication of reports for treatment of numerous conditions in the Community that have been submitted by the applicant in module 5 of the Common Technical Document (CTD).

The majority of data submitted supporting efficacy and safety with dexamethasone in the indications being sought have been obtained with tablet formulations. This corresponds to over 180 literature reports (RCTs; Reviews, Monographs (Martindale etc)) in the CTD. Therefore, a huge volume of efficacy and safety data exists for the dexamethasone pharmaceutical substance. In addition, a few literature reports (CTs) on the efficacy and safety of dexamethasone in oral solution/syrup have been submitted in the following indications applied for:

- Treatment of non-endocrine corticosteroid responsive conditions (for e.g. Croup; 7 CTs with a collated n number= 1586; in children)
- Asthma (1 CT; n=309; in children)
- Prevention of nausea and vomiting and treatment of cancer with oncolytics that have a serious emetic effect (1 Ct; n=43; in adults).

Literature data available on the various routes of administration for the same treatment show that dexamethasone is equally effective via any administration route.

The literature data provided showed that dexamethasone has a broad therapeutic index. Doses above 40 mg have been used in clinical practice and are recommended in acute/severe clinical conditions for short durations. This gives a tolerable dose range of more than 80-fold the starting dose.

In addition, the posology applied for recommends dose-titration for individual patients based on clinical response. A fixed dose level of dexamethasone (mg basis or mg/kg basis) is generally not recommended nor used in the therapeutic setting.

The bibliography supports the well established use of dexamethasone substance in different tablet formulations, and the different authorized immediate release tablet formulations have a similar posology.

It was therefore concluded by the CHMP that efficacy and safety of dexamethasone active substance in the therapeutic indications applied for had been sufficiently demonstrated by the provided literature.

From the literature data provided by the Applicant, it was shown that there were no significant differences between the bioavailabilities of immediate release tablet formulations and elixir formulations of dexamethasone (irrespective of the elixir formulation used). In addition, the limited number of published studies that used a solution formulation used a similar posology to the tablet formulation.

However, as information on the composition of the dexamethasone syrup, elixir or oral solution investigated in the provided studies was missing in all articles, some concerns were raised on whether those data could be considered as sufficient to allow bridging of the data between the tablets and the oral formulation applied for.

Additional bridging data (or its absence fully justified) between the bibliographic data and the proposed pharmaceutical product were therefore requested to the Applicant during the decentralised and the CMD(h) referral procedures.

BCS-based biowaiver

As a justification for not providing bioequivalence study to bridge the data submitted on the tablet formulation and the oral solution formulation applied for, the Applicant applied for a BCS (Biopharmaceutics Classification System)-based biowaiver.

The BCS-based biowaiver approach is meant to reduce in vivo bioequivalence studies. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

According to the Appendix II of the "Guideline on the investigation of bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr)", applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

Data on the solubility and on the absorption and permeability of dexamethasone were provided by the Applicant during the decentralised and the CMD(h) referral procedure to show that Dexamethasone Alapis 0.4 mg/ml met all criteria for a BCS-based biowaiver.

1. Solubility data

To demonstrate the high solubility of dexamethasone tablets, the Applicant has submitted supportive dissolution data using 3 pHs (1.2, 4.5 and 6.8), in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr). The dissolution results showed that EU sourced dexamethasone tablets 1 mg release >80% within 10 minutes and therefore were expected to behave similarly to dexamethasone oral solutions in humans.

From a pharmacokinetic perspective, the release of dexamethasone from tablets is considered to be immediate (>80% within 10 minutes). The availability of dexamethasone in the stomach can therefore be considered similar between dexamethasone immediate release tablets and dexamethasone oral solution.

2. Absorption/Permeability data

The applicant provided literature data on the absorption and permeability of dexamethasone.

It was shown in the published literature that dexamethasone has a high permeability over 60%. The high permeability of dexamethasone is characteristic of its pharmacological class (corticosteroids), which are generally accepted to be readily absorbed from the gastrointestinal tract (Czock et al., 2005; Martindale, 2007).

In addition, although no comparative bioavailability studies between the tablet and the oral solution exist in the literature, the bioavailabilities of dexamethasone tablets and elixir in man were evaluated by 3 model-independent methods of pharmacokinetic analysis employing plasma and urinary values as determined by radio-immune assay. There were no significant differences among the results determined by the 3 methods nor between the respective availabilities of the two formulations; the latter averaged 82.6 +/- 17.7% for the elixir formulation and 78.0 +/- 12.1% for tablets (Duggan et al., 1975). Elixirs are sweetened hydro-alcoholic oral solutions that are specially formulated for oral use in infants and children (Strickley, 2004). Therefore, from a pharmaceutical perspective, elixirs are a type of oral solutions and are expected to behave in vivo as such.

Moreover, in order to rank dexamethasone, or its sodium phosphate salt, in solid and oral pharmaceutical dosage forms, into a low or high permeable classification at different pHs, the Applicant used in-house parallel artificial membrane permeability assay (PAMPA) analysis techniques using PVDF membranes.

In addition, the effect of the excipients of solid and liquid dosage forms on Dexamethasone permeability was investigated and finally, results were correlated with bibliographic data.

Formulating liquid or solid dosage forms containing dexamethasone either as base or sodium phosphate salt did not affect active ingredients' permeability classification and thus remained highly permeable. Similarly, the specific excipients used for the preparation of oral liquid and solid dosage forms of Dexamethasone containing finished products, did not affect Dexamethasone permeability classification and thus remained highly permeable.

These findings were considered to be in line with existing literature data, where dexamethasone is classified as a highly permeable drug by using similar in-vitro techniques. Specifically, Nakao et al. (Nakao et al., 2009) reported Log Pe values of dexamethasone to be -5.7 using PAMPA analysis while, Artursson et al. (Artursson et al., 1991) found Log Pe to be -4.9 (Log 12.5 x 10-6) using Caco-2 monolayer cell analysis.

Finally, it has been reported that the percentage of Fraction Absorbed (%FA) in humans is about 95 to 100 for dexamethasone, which is in a high agreement with in vitro results (Balimane et al., 2008, Balimane et al., 2006, Toth et al., 1999, Dawe et al., 1997, van de Waterbeemd et al., 2003) providing so further justification for the suitability of the tests involved.

It can be concluded from those data that dexamethasone is a highly permeable active substance, subject of an extensive first pass effect.

3. Role of the excipients

As per Appendix II of the “Guideline on the investigation of bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr”, specifically relating to oral solutions, “if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or in vivo stability of the active substances, a bioequivalence study should be conducted, unless the difference in the amounts of these excipients can be adequately justified by reference to other data”.

The main excipient that could affect the bioavailability of dexamethasone and is present in the Applicant's oral solution is sorbitol. Sorbitol is widely used as excipient in pharmaceutical products. In oral solutions sorbitol is used a) due to the pleasant sweet taste and the feeling of cool that provides, b) as a solvent, c) as a substitute of sugar, d) as a stabilization agent and e) due to its property to prevent crystallization around the bottle stopper, and is present in many oral solutions. Sorbitol is not well absorbed in the gastrointestinal (GI) tract. Additionally, it increases the osmotic pressure in the intestine, which changes the flux of water in the GI tract. This osmotic stress can change the gastric emptying time and the intestinal transit times through both the upper and lower parts of the intestine. Transit times in the GI tract can affect drug absorption.

According to the Applicant, the amount of sorbitol present in 5 ml of Dexamethasone Alapis oral solution is 700 mg, which is less than the required amount of sorbitol to affect the gastrointestinal transit. Therefore, the presence of sorbitol in the formulation is not expected to have an effect on the gastrointestinal transit.

The presence of Maltitol was also noted. This excipient, a sugar alcohol used as a sugar substitute, is hydrolysed to glucose and sorbitol. Although it is hydrolysed to sorbitol, its slow hydrolysation diminishes the effect of sorbitol. The effect of maltitol to the gastrointestinal motility and permeability is therefore unclear.

As the other excipients contained in the drug product applied for have no impact on the gastrointestinal motility or drug permeability, it was concluded that none of the excipient contained in the drug product would influence the absorption of Dexamethasone Alapis 0.4 mg/ml oral solution.

4. Biopharmaceutical Classification of Dexamethasone

Literature data showed that dexamethasone can be classified as Class I compound according to BCS criteria, e.g. it is a high solubility, high permeability drug.

The PAMPA data obtained by the Applicant indicated that dexamethasone as an active substance was classifiable as a Class III drug (results comparable to published literature data).

Dexamethasone can therefore be classified as a BCS-class I/III active substance.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.4. Recommendation

Most of the literature provided by the Applicant concerned the administration of an oral solid dosage form, i.e. tablet. In order to extrapolate efficacy and safety data from these studies to the oral solution formulation applied for, the Applicant provided data that showed that irrespective of immediate release oral dosage formulation (tablet or solution), the bioavailability of dexamethasone in terms of extent and rate of absorption, was similar.

Although the "Guideline on the investigation of bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr" states: "In those cases where the test product is an oral solution which is intended to be bioequivalent

to another immediate release oral dosage form, bioequivalence studies are required", the application of a BCS-based biowaiver to bridge data from different pharmaceutical forms was considered to have been adequately justified from a scientific point of view, by provision of PAMPA data, literature and dissolution data, demonstrating that dexamethasone drug substance has biopharmaceutical characteristics of BCS Class I/III, and that the excipients have no adverse affects on bioavailability.

The CHMP therefore agreed that the bibliographic data provided for the tablet may be bridged to dexamethasone sodium phosphate used in the oral solution.

The strength and quality of evidence gathered from the above information is considered adequate for a medicinal product with a well established and broad therapeutic index as dexamethasone.

The Summary of Product Characteristics adopted during the procedure is considered to address adequately the safety concerns of this medicinal product.

2.5. Conclusions and benefit risk assessment

In conclusion, the CHMP considered the provided data as sufficient to support the applicant's claim that the bibliographic data for the tablet may be bridged to dexamethasone sodium phosphate used in the oral solution and therefore, the literature data provided on this application do support the safety and the efficacy of the product in the sought indications.

Based on:

- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the benefit/risk ratio of Dexamethasone Alapis 0.4 mg/ml is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.