ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

Scientific conclusions

Overall summary of the scientific evaluation of Dexamethasone Alapis

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 objecting Concerned Member State raised a potential serious risk to public health as it considered that the literature data on dexamethasone tablets that had been 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 concerns raised about bridging data.

At Day 60 of the CMD(h) procedure, since no agreement could be reached, the procedure was referred to the CHMP. The CHMP assessed the dossier and the available data, including the issues raised by the objecting CMS.

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 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 (Randomized Clinical Trials (RCTs); Reviews, Monographs (Martindale etc.). 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
- Asthma
- Prevention of nausea and vomiting and treatment of cancer with oncolytics that have a serious emetic effect.

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

The bibliography provided was considered sufficient to support the well established use of dexamethasone substance in different tablet formulations. It also showed that dexamethasone had a broad therapeutic index.

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.

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.

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.

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.

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.

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.

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 met all criteria for a BCS-based biowaiver.

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 parallel artificial membrane permeability assay (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 in support of the application demonstrates the well-established use of dexamethasone sodium phosphate used in the oral solution and that a bioequivalence study was not necessary to show the relevance of the literature used in support of the pharmaceutical form concerned.

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

The Summary of Product Characteristics achieved during the Coordination group procedure was considered to address adequately the safety concerns of this medicinal product.

Grounds for positive opinion

Whereas,

- the Applicant has provided sufficient literature data to demonstrate well-established use of dexamethasone,

- efficacy and safety of dexamethasone has been adequately shown in the indications applied for

- adequate bridging data between the tablet formulation and the oral solution formulation have been provided by the Applicant,

the CHMP has recommended the granting of the marketing authorisation(s) for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of this Opinion.