

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

Scientific conclusions

Overall summary of the scientific evaluation of Okrido and associated names (see Annex I)

Okrido is an oral solution containing 6 mg/ml of the glucocorticoid prednisolone, as prednisolone sodium phosphate (PSP). The proposed indications for Okrido oral solution 6mg/ml include a wide range of conditions where symptomatic anti-inflammatory/ immunosuppressive therapy is required. The indications and posology are consistent with those of the cited reference medicinal product Prednisolone Tablets Sovereign (5 mg soluble tablet).

One of the key excipients in Okrido is sorbitol which is included as a sweetener and is present at a concentration of 500 mg/ml (total amount at the highest dose being 8.3g) in the medicinal product. Sorbitol is a non-absorbable sugar alcohol that is used in 'sugar-free' formulations because it does not crystallise around the bottle opening and cap. The cited reference medicinal product Prednisolone Tablets Sovereign (5 mg soluble tablet), does not contain sorbitol and is recommended to be dissolved in water at the time of administration.

The mutual recognition marketing authorisation application (MAA) for Okrido was submitted in the UK as a generic medicinal product under article 10(1) of Directive 2001/83/EC, and the marketing authorisation was granted by the UK on the basis of a biowaiver. However, during the mutual recognition procedure (MRP), the member states Germany and The Netherlands were of the view that the claim for a BSC-based biowaiver had not been adequately justified, and that on this basis Okrido could be a potential serious risk to public health. During the CMD-h referral procedure that followed, no consensus could be reached as The Netherlands maintained their objection. The CMDh therefore referred the matter to the CHMP through an Art 29(4) referral procedure.

The data submitted by the MAH in support of this application were assessed, and a summary is provided below:

- Solubility and dissolution

The active ingredient in Okrido, prednisolone sodium phosphate, is 'freely soluble in water' (Ph Eur). According to the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev 1), a drug substance is considered as highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C. For Okrido, this equates to 0.536 mg/ml for prednisolone phosphate. The MAH has provided solubility data which show that prednisolone sodium phosphate (PSP) is completely dissolved in water at a concentration of ~ 8.9 mg/ml, and that prednisolone remains in solution across the pH range of 1 to 8.

Solubility and/or dissolution are therefore not considered to be a limiting factor in terms of *in vivo* absorption.

- Permeability/Absorption

The applicant has submitted the results of an *in vitro* investigation of the permeability of prednisolone using validated methodology involving the Caco-2 monolayer cell model.

The results indicate that the permeability of prednisolone is high, whether applied directly, as Okrido or prednisolone soluble tablets. Following transport across the Caco-2 cell monolayer, prednisolone was recovered in the range of 84% to 106% of the applied dose, whether as prednisolone sodium

phosphate, Okrido oral solution or the reference medicinal product Prednisolone Sovereign soluble tablet. This is in accordance with bioavailability literature data of prednisolone.

In summary, the results of the in vitro investigation of the permeability of prednisolone using the Caco-2 cell model showed that prednisolone exhibits high permeability, characteristic of BCS class I substances, and also that the permeability of prednisolone is not affected by the excipient sorbitol in Okrido. The permeability data is reflective of the available literature data, which indicate that prednisolone is rapidly and almost completely absorbed passively from the upper gastrointestinal tract.

- Excipients

The excipient sorbitol is available in Okrido (500 mg/ml) and not in the reference medicinal product. Considering that the reference medicinal product and Okrido are oral solutions at the time of administration, the following provision of Appendix II of the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98, Rev.1) is applicable:

'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 substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers (see Appendix III, Section IV.2 Excipients).'

The MAH has submitted published clinical data (Lucas-Bouwmann 2001¹) to support the lack of a clinically relevant effect of sorbitol on prednisolone absorption. Crushed prednisolone tablets were compared to prednisolone syrup (with sorbitol), in children with acute asthma, using dyspnoea as clinical end point. The authors of the study found that there was no difference in dyspnoea scores and concluded therapeutic equivalence, implying also bioequivalence.

The MAH has also provided the abstract of an observational study (Staubach 2010²) to support the clinical efficacy of the oral prednisolone solution containing sorbitol on emergency care patients presenting with urticaria and/or Quincke's oedema. Efficacy was measured by patients and physician by rating resolution of symptoms as well as safety and tolerability. The rapid resolution of symptoms was comparable to i.v. therapy with prednisolone, and safety and tolerability were shown.

The Scientific Expert Statements provided by the MAH, suggest that prednisolone is rapidly and almost completely absorbed passively from the upper gastrointestinal tract (stomach, duodenum and small intestines) before reaching the colon, where sorbitol at a sufficiently high concentration may exert some osmotic laxative effect.

It is acknowledged that sorbitol can increase gastrointestinal motility, as a consequence of its osmotic effect, thereby reducing gastrointestinal transit time, which in turn can reduce drug absorption. Indeed Chen et al³ (2007)⁴ showed that in the presence of sorbitol, C_{max} and AUC of ranitidine (BCS class III, low permeability substance) were significantly reduced while only the C_{max} of metoprolol (BCS class I

¹ M E Lucas-Bouwman, R J Roorda, F G A Jansman, P L P Brand (2001). Crushed prednisolone tablets or oral solution for acute asthma? Arch Dis Child; 84:347-348.

² Staubach P (2010). Anwendungsbeobachtung der NRF-Rezeptur „Prednisolon-Saft“ an der Universitäts-Hautklinik Mainz. Symposium der GD-Fachgruppe Magistralrezepturen: Neues zur Qualitätssicherung dermatologischer Rezepturen

³ Chen M, Straughn A, Sadrieh N. et al (2007). "A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol". Pharm. Res. 24, 73-80.

⁴ Chen M, Straughn A, Sadrieh N. et al (2007). "A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol". Pharm. Res. 24, 73-80.

high permeability substance) was similarly affected. However taking into account the high solubility, and the rapid and almost complete absorption along the entire length of the small intestine, the CHMP was of the view that the amount of prednisolone absorbed will not be significantly affected by decreased residence time of the administered dose in any segment of the intestine, or reduced intestinal residence time overall.

Recommendation

Both Okrido and the reference product are dissolved in water before administration and are considered to be oral solutions, which exhibit high solubility across the gastrointestinal physiological pH range. Solubility and dissolution are not considered to be a limiting factor in terms of *in vivo* absorption.

Permeability has been investigated using *in vitro* Caco-2 monolayer cell model and the results showed that prednisolone exhibits high permeability characteristic of BCS class I substances, and also that the permeability of prednisolone is not significantly affected by the excipient sorbitol in Okrido. The permeability data is reflective of the available literature, which indicates that prednisolone is rapidly and almost completely absorbed across the upper gastrointestinal tract.

Based on the submitted *in vitro* Caco-2 monolayer cell model (permeability assay model), published literature and the oral explanation by the MAH on 26 June 2013, the CHMP considers that the biowaiver is acceptable, and therefore concluded that the benefit-risk balance for Okrido in the applied indications is favourable.

Grounds for positive opinion

Whereas,

- The Committee considered the notification of the referral triggered by the United Kingdom under Article 29(4) of Directive 2001/83/EC;
- The Committee reviewed all the data submitted by the marketing authorisation holder to address the potential serious risk to public health with regard to the efficacy and safety for Okrido 6 mg/ml oral solution.
- The Committee considered that the biowaiver applied in place of an *in vivo* bioavailability study for Okrido was acceptable as:
 - Both Okrido and the reference product are dissolved in water before administration and are considered to be oral solutions, which exhibits high solubility across the gastrointestinal physiological pH range. Therefore solubility and/or dissolution are not considered to be a limiting factor in terms of *in vivo* absorption.
 - Prednisolone (as sodium phosphate) exhibits high permeability as determined by the *in vitro* Caco-2 cell permeability model, and the permeability of Okrido is unaffected by the excipient sorbitol.
 - Prednisolone is rapidly and almost completely absorbed in the upper gastrointestinal tract.
- The Committee also noted the literature data that was submitted, which showed that sorbitol in oral prednisolone solutions would not exert a clinically relevant effect in terms of efficacy and safety, although recognised that this literature was less relevant to the consideration of the biowaver.
- The Committee therefore concluded that biowaver was justified and the risk-benefit balance for Okrido in the applied indications is favourable,

the CHMP has recommended the granting of the marketing authorisation 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.