Annex II

Scientific conclusions and grounds for refusal

Scientific conclusions

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

The proposed indications for Levothyroxine Alapis are for: the treatment of hypothyroidism (congenital or acquired, including diffuse non-toxic goiter), hypothyroidism forms of Hashimoto's thyroiditis and thyroid carcinoma. The proposed patient populations are: adults, children over 12 years (in the treatment of diffuse non-toxic goitre), and neonates and infants (with congenital hypothyroidism).

The active substance levothyroxine, is an established active substance described in the European Pharmacopoeia. Levothyroxine Alapis is an oral drop solution containing levothyroxine sodium as active substance (100 mcg/ml). The excipients are glycerol, propylene glycol, ethanol and purified water, which comply with the respective Ph.Eur monographs.

The decentralised marketing authorisation application for the medicinal product Levothyroxine is a well-established use application according to Article 10(a) of Directive 2001/83/EC. This is a bibliographic application that refers to literature concerning several levothyroxin tablet formulations and solutions and thus no reference is made to a single unique formulation.

Since no consensus could be reached on the issues relating to medication errors due to the method of administration of the oral drops and the safety of excipients ethanol and propylene glycol in the paediatric population, the CMDh referred the matter to the CHMP under Article 29(4) of Directive 2001/83.

In light of the Applicant's failure to provide responses to the CHMP list of questions during the Article 29(4) referral procedure, the assessment was carried out on the data made available during the decentralised procedure and the CMDh referral procedure.

Medication errors caused by the administration device (dropper insert)

Initially two different dropper inserts resulting in different drop sizes that would count up to 40 drops was proposed by the Applicant. However this was not accepted due to the risk of dosing errors.

The applicant then proposed to use:

- a **dropper insert** for doses between 12.5 µg and 50 µg (5 to 20 drops) and
- a 3 mL **oral syringe** for doses between 50 µg and 200 µg (0.5 to 2 mL)

According to the proposed Summary of Product Characteristics (SmPC), the dropper insert will be mainly used for administration to paediatric patients as well as for initial dosing of adults and children over 12 years.

The possible medication errors caused by the dropper insert were discussed by the CHMP:

Inaccuracies due to improper dropper orientation

Levothyroxine Alapis is a solution with low viscosity, which gives a fast drop rate. Therefore any deviation from vertical orientation, such as an attempt to slow the drop rate will result in inaccurate drop volume. Published literature[1] highlights the potential for significant variability in both drop rate and volume for low viscosity solutions such as this product, where bottle orientation is not vertical.

[1] An assessment of dose-uniformity of samples delivered from paediatric oral droppers, A.J. Nunn et al; Journal of Clinical Pharmacy and Therapeutics (2004) 29, 521–529

Deviation from a vertical position is more likely in situations where the patient / carer is attempting to manage / slow the drop rate to enable a relatively high number of drops to be counted.

Inaccuracies due to miscounting

The dosing errors due to the difficulty in accurately counting a large number of drops per dose (up to 20 drops) of Levothyroxine Alapis solution also remain a concern.

It is also noted that the proposed package leaflet (PL) recommends that the drops are not administered directly to the patient, but should first be delivered to a spoon. This represents an impractical means of dosing babies and small infants, and will result in further variability in dosing volumes associated with use of a second administration device.

Levothyroxine Alapis, which is formulated as a highly concentrated solution of a very potent active substance, is associated with adverse events with chronic over-dosing - particularly cardiovascular. Chronic under-dosing has consequences to normal brain development of children.

In conclusion given that Levothyroxine Alapis is a highly concentrated solution containing 100 mcg/ml the dropper device is considered to be unsuitable due to inaccuracies resulting from improper dropper orientation and miscounting, especially for paediatric initial doses less than 25 mcg.

The absence of robust user testing with representative members of the general public provides no reassurance that this dropper device will prove manageable and accurate in practice.

Safety of excipients (ethanol / propylene glycol) in paediatric population

The excipients used in Levothyroxine Alapis are ethanol, propylene glycol, glycerol and water and comply with the Ph. Eur monographs. Both ethanol and propylene glycol are initially metabolised by alcohol dehydrogenase. Alcohol dehydrogenase preferentially metabolises ethanol prior to metabolising other alcohols, including propylene glycol. Since both propylene glycol and ethanol share a common metabolic pathway the combination of ethanol and propylene glycol is a concern.

In light of the failure to provide responses to the CHMP list of questions, , the available information was not considered to be sufficient to address the safety concerns of the chronic use of ethanol and the propylene glycol, in particular in the paediatric population.

Ethanol

Levothyroxine Alapis contains 200mg/ml of ethanol per dose. The guidance “Guideline on the excipients in the label and the package leaflet of medicinal products for human use” states that if the content of ethanol is 100 mg – 3g per dose, the following should be stated in the PL:

‘This medicinal product contains < > vol % ethanol (alcohol), i.e. up to < > mg per dose, equivalent to < > ml beer, < > ml wine per dose.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.’

Newborn infants, and children are not able to metabolize ethanol as efficiently as adults; as a consequence, they may be at higher risk of both acute and chronic alcohol-related toxicities. As there is limited information on safe ethanol concentrations in paediatric formulations intended for chronic use, there are concerns with regard to chronic use of Levothyroxine Alapis in neonates/children, as ethanol represents an additional insult to brain development that is already compromised by congenital hypothyroidism.

In addition there are also concerns in patients with hepatic impairment, epilepsy and in vulnerable adults such as those suffering from alcoholism.

As ethanol is used to solubilise levothyroxine, its use is not considered to be essential in this formulation, based on the relatively poor solubility of levothyroxine in ethanol when compared to propylene glycol.

Propylene glycol

Although propylene glycol is widely used as an excipient in oral and injectable medicines, literature data on its safety in children when administered chronically is sparse. The study by MacDonald et al[2], seems relevant as daily doses of propylene glycol similar to what can be expected from Levothyroxine Alapis were studied in one of the study arms. Two groups of infants were treated with two doses of propylene glycol; 0.3 g/day and 3 g/day in an IV multivitamin solution, during two consecutive 19-month periods in a retrospective design. Despite the shortcomings of this study the data suggest a dose-dependent trend towards a higher incidence of seizures with higher doses of propylene glycol. There was a significant difference in the occurrence of clinical seizures (P = .021). More seizures occurred with the higher dose of propylene glycol, where 33% of the infants had seizures, vs only 14% of infants who received the lower dose of propylene glycol.

Combination of ethanol and propylene glycol

As mentioned previously, both ethanol and propylene glycol are initially metabolised by alcohol dehydrogenase. Alcohol dehydrogenase preferentially metabolises ethanol prior to metabolising other alcohols, including propylene glycol. Therefore, co-administration of ethanol and propylene glycol can lead to raised and potentially toxic levels of the latter.

Therefore there are major safety concerns due to the chronic use of the combination of ethanol and propylene glycol in neonates/children.

Based on the above, the CHMP considers that the safety concerns relating to Levothyroxine Alapis that were raised during the decentralised procedure and the CMDh referral procedure have not been sufficiently addressed.

Grounds for refusal

Whereas

- The Committee considered the notification of the referral triggered by the United Kingdom under Article 29(4) of l Directive 2001/83/EC.
- The Committee reviewed all the data that was available to address the potential serious risk to public health, in particular with regard to the safety of Levothyroxine Alapis 100 microgram/ml oral drops solution.
- The Committee was of the opinion that there was an unacceptable risk of medication error due to the dropper insert, where the inappropriate orientation of the dropper insert would result in inaccurate and variable drop volume. Inaccuracy due to the miscounting of the large number of drops administered also contributes to the risk of medication error. Levothyroxine Alapis, which is a highly concentrated solution of a highly potent medicinal product, is associated with adverse events with chronic over-dosing - particularly cardiovascular events. Chronic under-dosing has consequences to normal brain development of children. Therefore the risk of medication error was considered to be a potential serious risk to public health.

[2] (Pediatrics Vol. 79 No. 4 April 1987)(2)

- The Committee was of the opinion that the chronic co-administration of the proposed quantities of the excipients ethanol and propylene glycol in children remains a safety concern. In addition there are concerns in vulnerable adults such as those suffering from alcoholism, as well as in patients with hepatic impairment and epilepsy.
- The Committee concluded that the risk-benefit balance of Levothyroxine Alapis is therefore not considered to be favourable.

And therefore the CHMP recommended the refusal of the granting of the marketing authorisation for Levothyroxine Alapis and associated names (see Annex I).