



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report for Levothyroxine Alapis and associated names

Referral under Article 29(4) of Directive 2001/83/EC

INN of the active substance: levothyroxine sodium

Procedure no: EMEA/H/A-29/1328

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



Table of contents

1. Background information on the procedure	3
1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure	3
1.2. Notification of an official referral for arbitration	3
2. Scientific discussion during the referral procedure.....	3
2.1. Introduction.....	3
2.2. Critical evaluation.....	4
2.3. Risk management plan.....	7
2.4. Recommendation	7
2.5. Conclusions and benefit risk assessment	7

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 (DCP) of Levothyroxine Alapis 100 microgram/ml oral drop solution and associated names on 6 August 2010.

The application was submitted to the reference Member State (RMS): The Netherlands and the concerned Member States (CMS): Belgium, Bulgaria, Cyprus, Germany, Greece, Malta, Portugal, Romania and United Kingdom. However at the time of this opinion a valid application does not exist in Bulgaria and Germany.

The Decentralised procedure NL/H/2090/001/DC started on 6 October 2010.

On day 210, UK's major issues on quality and safety, remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, by the Netherlands on 3 November 2011. The CMD(h) procedure was initiated on 28 November 2011. Day 60 of the CMD(h) procedure was on 26 January 2012 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, to the CHMP was made by the Netherlands on 26 January 2012, with a subsequent addendum on 7 February 2012. United Kingdom raised public health objections related to possible medication errors due to the administration device(s) and the safety of the chronic use of the excipients ethanol and propylene glycol, particularly in children.

2. Scientific discussion during the referral procedure

2.1. Introduction

Thyroxine, or 3,5,3',5'-tetraiodothyronine (often abbreviated as T4), is the major hormone secreted by the follicular cells of the thyroid. Thyroxine is involved in controlling the rate of metabolic processes in the body and influencing physical development. It is thought that their principal effects are exerted through control of DNA transcription and protein synthesis.

Levothyroxine sodium was initially manufactured as synthetic T4 in 1958 and it was first introduced into the market as early as 1962. Levothyroxine is available in the EU as oral solid formulations (tablets and soft capsules) and oral solutions.

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 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 treatment of any thyroid disorder is determined on an individual basis, taking account of clinical response, biochemical tests and regular monitoring.

The presented 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 levothyroxine tablet formulations and solutions and thus no reference is made to a single unique formulation.

2.2. Critical evaluation

The literature data shows that oral solutions and tablet formulations of levothyroxine have in general a comparable bioavailability, taking into account the excipients used in the current formulation. The issue of comparable bioavailability of Levothyroxine Alapis with oral solution and tablet formulations was agreed on during the CMDh discussion.

However two remaining 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 could not be resolved during the CMDh discussion.

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 through an Article 29(4) referral procedure.

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 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 literature¹ 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. 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 (upto 20 drops) of Levothyroxine Alapis solution also remain a concern.

It is also noted that the package leaflet (PL) requires 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

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

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 administration 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.'

Newborns, 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 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

Propylene glycol is an alcohol solvent widely used to prepare drug formulations. Like ethanol, it is rapidly absorbed from the GI tract and is metabolised in the liver (to pyruvic acid and lactic acid) and

also excreted unchanged in urine. Propylene glycol is estimated to be one-third as intoxicating as ethanol. 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 al², 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.

The purpose of the study by MacDonald et al was to compare selected clinical problems in small premature infants receiving IV nutrition during a 19-month period, with clinical findings in a group of small premature infants who received IV nutrition during the preceding 19-month period in a retrospective design. The major source of propylene glycol for these infants was an IV multivitamin solution, MVI-12 (Armour Pharmaceutical Co). The infants were treated with two doses of propylene glycol; 0.3 g/day and 3 g/day. The study was divided into two time periods - A and B:

Period A included the dates from Dec 1, 1979, to July 1, 1981, when all infants received 1 mL of MVI concentrate per day (1 mL of MVI concentrate contained 300 mg of propylene glycol which is roughly equal to the amount of propylene glycol in 1 mL of Levothyroxine Alapis, delivering 100mcg of levothyroxine). The infants treated during this earlier period received a lower daily dose of propylene glycol.

Period B commenced on July 1, 1981, and ended on Jan 3, 1983. In this second period, MVI-12, 10 mL was routinely given to all infants who received IV nutrition. These children received 3 g/d of propylene glycol, ie, ten times the amount received by the infants in period A.

Given the retrospective design of the study, the sample size mismatch between the 2 groups, lack of synchronicity between the 2 study arms and lack of a placebo (or no treatment) comparator group, the results are interpreted with caution. It is also noted that although 14 days has been mentioned as the minimum duration of treatment, the mean or the maximum duration of treatment has not been given in the paper.

Considering the ethical barriers of conducting such studies prospectively, the data are nevertheless of value and suggest a dose dependent trend towards 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 in period B, when 33% of the infants had seizures, vs only 14% of infants in period A.

As a placebo group was not included, it is not clear how the lower dose group would compare to placebo in terms of the overall incidence of adverse reactions and, in particular, the incidence of seizures.

It has been suggested that preterm babies may be at increased risk for health problems because they cannot metabolise propylene glycol; this could lead to accumulation and adverse events such as serious heart, kidney, or breathing problems. In 1973, WHO set an acceptable daily intake of 0-25 mg/kg for propylene glycol. However it is important to stress that propylene glycol is excreted by the kidneys, and because renal function is closely related to gestational age, the limit of "up to 25 mg/kg" is likely to be significantly lower for preterm infants.

Combination of ethanol and propylene glycol

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.

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

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

2.3. Risk management plan

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

2.4. Recommendation

Levothyroxine Alapis is a highly concentrated solution of a highly potent medicinal product, which requires administration by means of a dropper insert for doses up to 50mcg, comprising up to 20 drops. The risk of medication error, where the inappropriate orientation of the dropper insert would result in inaccurate and variable drop volume, and inaccuracy due to the miscounting represent major safety concerns, relating to adverse events with chronic over-dosing - particularly cardiovascular events. In addition, there are consequences to normal brain development of children with chronic under-dosing.

Levothyroxine Alapis also contains the excipients ethanol and propylene glycol, both of which raise safety concerns, particularly in children. Insufficient data has been provided to support their safe use in the quantities proposed, for use in the oral solution of Levothyroxine Alapis.

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.

2.5. Conclusions and benefit risk assessment

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 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.
- 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).