14 January 2013
EMA/659681/2012 Rev1.
EMEA/H/A-29/1328

Questions and answers on Levothyroxine Alapis and associated names (levothyroxine sodium, oral drops, 100 microgram/ml)

Outcome of a procedure under Article 29 of Directive 2001/83/EC

On 18 October 2012, the European Medicines Agency completed an arbitration procedure following a disagreement among Member States of the European Union (EU) regarding the authorisation of the medicine Levothyroxine Alapis. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Levothyroxine Alapis do not outweigh its risks, and the marketing authorisation cannot be granted in the Netherlands or in the following EU Member States: Belgium, Bulgaria, Cyprus, Germany, Greece, Malta, Portugal, Romania and United Kingdom.

What is Levothyroxine Alapis?

Levothryoxine Alapis is a medicine that contains the active substance levothyroxine sodium. It was to be available as oral drops (100 microgram/ml). The active substance in Levothyroxine Alapis, levothyroxine sodium, is a synthetic form of the hormone thyroxine. Thyroxine is normally produced in the body by the thyroid gland in the neck. It controls many body functions, mainly to do with growth and energy. Levothyroxine Alapis was intended to be used to treat:

- conditions in which the thyroid gland is underactive (hypothyroidism, including diffuse non-toxic goitre) and so does not make enough thyroxine for the body's needs;
- a condition known as Hashimoto's thyroiditis, in which the immune system (the body's natural defences) attacks the thyroid causing it to swell and preventing it from working properly;
- thyroid cancer.

Why was Levothyroxine Alapis reviewed?

Alapis S.A. submitted an application for Levothyroxine Alapis to the Dutch medicines regulatory agency for a decentralised procedure. This is a procedure where one Member State (the 'reference Member State', in this instance the Netherlands) assesses a medicine with a view to granting a marketing authorisation that will be valid in this country as well as in other Member States (the 'concerned

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Member States', in this instance Belgium, Bulgaria, Cyprus, Germany, Greece, Malta, Portugal, Romania and United Kingdom).

However, the Member States were not able to reach an agreement and the Dutch agency referred the matter to the CHMP for arbitration on 26 January 2012.

The grounds for the referral were concerns raised by the UK related to the dropper insert as a proposed administration device, due to the large number of drops that may be required and concerns about its accuracy in delivering the required dose. This could potentially lead to medication errors and pose a risk to public health. In addition there were concerns over the safety of the combined long-term use of the ingredients ethanol and propylene glycol at the proposed concentrations, particularly in children.

What are the conclusions of the CHMP?

Based on evaluation of the currently available data and the scientific discussion within the Committee, the CHMP agreed that there was a risk that the dropper used for delivery might deliver variable doses, and that large numbers of drops might be hard to count. Since the solution is highly concentrated and the active substance highly potent, there was an unacceptable risk of serious medication errors. In addition, there remained concern over the safety of the long-term use of the ingredients ethanol and propylene glycol in children, and some groups of adults such as those with alcoholism. Therefore the CHMP concluded that the benefits of Levothyroxine Alapis do not outweigh its risks, and that the marketing authorisation should not be granted in the concerned Member States.

The European Commission issued a decision on 14 January 2013.