10 December 2020
EMA/CHMP/532756/2020
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg (and additional strengths) and 200 mcg product-specific bioequivalence guidance' (EMA/CHMP/176098/2020)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Merck Healthcare KGaA
2	BERLIN-CHEMIE AG

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	It is assumed that for topics not discussed in this guideline, the general BE guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** is applicable, and if this is correct, it is proposed to include a reference to the general guideline	This is explained in the 'Concept paper on development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013)' that is available on the product specific guideline landing page https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/product-specific-bioequivalence-guidance.
2	We do not agree with the proposed guidance paper "Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg (and additional strengths) and 200 mcg product-specific bioequivalence guidance" (EMA/CHMP/176098/2020). We do not consider levothyroxine containing medicinal products as critical dose drugs. In the standard clinical practice regular and routinely monitoring of laboratory parameters and clinical effectiveness takes place.	In most patients there is a sufficient margin between efficacy and toxicity, arguing against levothyroxine as a narrow therapeutic index (NTI) drug. In addition, acute overdosing with levothyroxine is not associated with substantial toxicity (for a BE study 600 mcg are administered), therefore, it cannot be labelled as NTI. However, it is also recognised that in a proportion of patients, levothyroxine may exhibit a steep efficacy-dose response, leading to loss of well-being with small changes in bioavailability. For example, elderly patients and patients with cardiac disease are more susceptible to the toxic effects of levothyroxine. It is well known that even small and clinically covert overdosing increases the risk of atrial fibrillation. Furthermore, levothyroxine replacement therapy needs to be carefully titrated during pregnancy to avoid an adverse impact on the course of pregnancy or foetal development.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		Many patients need careful titration of levothyroxine, e.g. in 12.5 mcg titration steps. It is therefore considered that, while there is insufficient justification to classify levothyroxine as an NTI drug, it should be considered a critical dose drug.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
22 - Analyte	1	**Comment:** Under "Analyte" plasma/serum is checked. Therefore, it is proposed to include "serum" in the recommendations regarding method for baseline adjustment. **Proposed change:** "Recommendations regarding method for baseline adjustment: Plasma**/serum** levothyroxine values […]"	Accepted.