10 December 2020
EMA/CHMP/176098/2020
Committee for Medicinal Products for Human Use (CHMP)

Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg and 200 mcg (and additional strengths within the range) product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)*	6 May 2020
Adopted by CHMP for release for consultation	28 May 2020
Start of public consultation	15 June 2020
End of consultation (deadline for comments)	30 September 2020
Agreed by Pharmacokinetics Working Party	19 November 2020
Adopted by CHMP	10 December 2020
Date for coming into effect	1st July 2021

*Experts of the Cardiovascular Working Party (CVSWP) were consulted on specific questions

Keywords	***Bioequivalence, generics, levothyroxine***

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Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)

BCS Classification	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Solubility characteristics are atypical with self-association to form aggregates, low intrinsic solubility and intrinsic dissolution rate.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Number of studies: One study at the highest strength.
	Other design aspects: A single supra-therapeutic dose of 600 mcg of test and reference product should be administered. Given that washout cannot be formally confirmed due to the presence of endogenous hormone, together with a long plasma elimination half-life, a minimum washout period of 35 days between treatment periods is recommended.

	☒ **parent** ☐ **metabolite** ☐ **both**
Analyte	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
	Recommendations regarding method for baseline adjustment: Plasma/serum levothyroxine values for pharmacokinetic analysis are recommended to be corrected for endogenous thyroxine by subtraction of the mean of three pre-dose plasma thyroxine concentrations (e.g. at 0.5 h, 0.25 h, and 0 h pre-dose) from the values obtained post-dose.
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max} **90% confidence interval:** 90.00 – 111.11% for AUC_{0-72h} and 80.00 – 125.00% for C_{max} **Background:** levothyroxine is a critical dose drug