



1 28 May 2020  
2 EMA/CHMP/176098/2020  
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75**  
5 **mcg, 100 mcg (and additional strengths) and 200 mcg**  
6 **product-specific bioequivalence guidance**  
7 **Draft**

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	
Adopted by CHMP	
Date for coming into effect	

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10 Comments should be provided using this [template](#). The completed comments form should be sent to  
11 [PKWPsecretariat@ema.europa.eu](mailto:PKWPsecretariat@ema.europa.eu)

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<b>Keywords</b>	<b><i>Bioequivalence, generics, levothyroxine</i></b>
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16 **Levothyroxine tablets 12.5 mcg, 25 mcg, 50 mcg, 75 mcg, 100 mcg (and additional**  
 17 **strengths) and 200 mcg product-specific bioequivalence guidance**  
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19 Disclaimer:

20 *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*  
 21 *a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.*

22 **Requirements for bioequivalence demonstration (PKWP)**

<b>BCS Classification</b>	<b>BCS Class:</b> <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> <b>Neither of the two</b>  <b>Background:</b> Solubility characteristics are atypical with self-association to form aggregates, low intrinsic solubility and intrinsic dissolution rate.
<b>Bioequivalence study design</b>  <i>in case a BCS biowaiver is not feasible or applied</i>	<b>single dose</b>  <b>cross-over</b>
	<b>healthy volunteers</b>
	<input checked="" type="checkbox"/> <b>fasting</b> <input type="checkbox"/> <b>fed</b> <input type="checkbox"/> <b>both</b> <input type="checkbox"/> <b>either fasting or fed</b>
	<b>Number of studies:</b> One study at the highest strength if the conditions for the additional strength biowaivers are fulfilled.
	<b>Other design aspects:</b> A single supra-therapeutic dose of 600 mcg of test and reference product should be administered.

	<p>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.</p> <p><input checked="" type="checkbox"/> <b>parent</b>   <input type="checkbox"/> <b>metabolite</b>   <input type="checkbox"/> <b>both</b></p>
<b>Analyte</b>	<p><input checked="" type="checkbox"/> <b>plasma/serum</b>   <input type="checkbox"/> <b>blood</b>   <input type="checkbox"/> <b>urine</b></p> <p><b>Enantioselective analytical method:</b>   <input type="checkbox"/> <b>yes</b>   <input checked="" type="checkbox"/> <b>no</b></p> <p><b>Recommendations regarding method for baseline adjustment:</b> Plasma 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.</p>
	<p><b>Bioequivalence assessment</b></p> <p><b>Main pharmacokinetic variables:</b> <math>AUC_{0-72h}</math> and <math>C_{max}</math></p> <p><b>90% confidence interval:</b> 90.00–111.11% for <math>AUC_{0-72h}</math> and 80.00–125.00% for <math>C_{max}</math></p> <p><b>Background:</b> levothyroxine is a critical dose drug</p>