



1 21 May 2024
2 EMA/CHMP/219378/2024
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Budesonide, prolonged release tablets, 9 mg product-**
5 **specific bioequivalence guidance**
6 **Draft**

Draft Agreed by Methodology Working Party (MWP)	23 April 2024
Adopted by CHMP for release for consultation	21 May 2024
Start of public consultation	25 June 2024
End of consultation (deadline for comments)	30 September 2024

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Keywords	<i>Bioequivalence, generics, budesonide</i>
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12 **Budesonide, prolonged release tablets, 9 mg product-specific bioequivalence guidance**

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14 Disclaimer:

15 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
16 marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

17 Requirements for bioequivalence demonstration (MWP)*

Bioequivalence study design	Single dose fasting and fed: 9 mg; healthy volunteers Background: 9 mg is the only available strength
	cross-over
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC8-20h, AUC20-48h, AUC0-t, AUC0-inf, Cmax Secondary parameters: AUC0-8h Background/justification: Partial AUCs should be based on the PK profile of the reference product and be related to the clinically relevant corresponding absorption site(s), considering the specific release characteristics.

	<p>Early partial AUC_{0-8h} as supportive (descriptive statistics only) parameter as mainly reflects absorption before site of action. Early AUC may be very variable and represents a relatively low percentage of the total absorption. Early absorption is also dependent on the events within the gastrointestinal tract such as variability in the gastric emptying.</p> <p>Two late partial AUCs to better characterise the shape of the plasma concentration versus time curve.</p>
	<p>90% confidence interval: 80.00– 125.00%</p> <p>To be noted: The requirements defined in the 'Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1)' should be applied i.e. Test and reference products should exhibit similar in vitro dissolution profiles in a battery of state-of-the-art experiments (QC media and buffers at pH 1.2, 4.5 and 6.8, but also in vitro methods simulating intraluminal pH-conditions, ionic buffer strength, physiological buffer composition, mechanical stress and residence times in the human GI tract, e.g. tests in the reciprocating cylinder apparatus simulating "average" fasted subjects and also a range of "patient-specific" patterns of pH-conditions and passage times with continuous and discontinuous passage through the small intestine). The choice of methods should be justified.</p> <p>In addition, comparable dissolution profiles in buffer at pH 7.2. In vitro studies of the release in alcohol solutions should also be performed.</p>

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* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}, C_{T,ss} and partial AUC. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.