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Committee for Medicinal Products for Human Use (CHMP)

Budesonide, gastro-resistant hard capsules, 3 mg, gastro-resistant granules, 9 mg product-specific bioequivalence guidance

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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 (MWP)*

Bioequivalence study design	**Single dose fasting and fed:** 3 mg for capsules, 9 mg for granules; healthy volunteers **Background:** 3 mg and 9 mg are the only available strengths for these different formulations
	cross-over
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{4-8h}, AUC_{8-24h}, AUC_{0-t}, AUC_{0-inf}, C_{max} **Secondary parameters:** AUC_{0-4h} **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.

	Early partial AUC_{0-4h} as supportive (descriptive statistics only) parameter as mainly reflects absorption before site of action. Early AUCs have been shown to be very variable and represent 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. Two late partial AUCs to better characterise the shape of the plasma concentration versus time curve.
	90% confidence interval: 80.00– 125.00%
	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. In addition, comparable dissolution profiles in buffer at pH 6.4. *In vitro* studies of the release in alcohol solutions should also be performed.

* 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}, $C_{\tau,ss}$ and $_{partial}$ AUC. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.