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Committee for Medicinal Products for Human Use (CHMP)

Asenapine sublingual tablets 5 and 10 mg product-specific bioequivalence guidance

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* This revision addresses textual changes in wording regarding dose proportionality in line with the ICH M13A guideline

Keywords	***Bioequivalence, generics, asenapine***

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Asenapine sublingual tablets 5 and 10 mg product-specific bioequivalence guidance

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:** asenapine maleate reaches the circulation primarily by absorption in the oral cavity, rather than by swallowing and absorption through the gastrointestinal tract. Therefore the product cannot be considered for a BCS based biowaiver.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers or patients in case of intolerability
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 5 and 10 mg. **Background:** The less than dose proportional pharmacokinetics of asenapine may be attributed to both limited solubility and limitations in the absorption capacity from the oral mucosa following sublingual

	administration. For drugs with a less than proportional increase in AUC and/or C_{max} with increasing dose over the therapeutic dose range due to limited drug solubility, bioequivalence should in most cases be established both at the highest strength and at the lowest strength, i.e. in this situation two bioequivalence studies are needed.
	Number of studies: two single dose studies
	Other critical aspects: no fluids to be administered 1 hour before or 1 hour after dosing. Clear description of procedures for administering the product, mouth rinse and checks etc. Procedures should be representative of normal conditions of use e.g. no special measures to prevent swallowing of drug that would not be applicable in normal clinical use.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and C_{max}
	90% confidence interval: 80.00– 125.00%

* 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}. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.