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Committee for Medicinal Products for Human Use (CHMP)

Lanreotide acetate, prolonged-release solution for injection in prefilled syringe 60, 90 and 120 mg product-specific bioequivalence guidance

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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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)*

Bioequivalence study design	**Single dose** **Background:** Taking into account the difficulties in performing a multiple dose study (e.g. 28 day dosing interval, multiple indications and limited target populations), as accumulation is not high and the single dose profile is captured over a prolonged period, a multiple dose study may be waived if the single dose PK is well characterised. Further analysis of the single dose data is therefore required to fully capture the pharmacokinetic profile.
	Parallel design **Background**: Due to the long half-life and for safety reasons the crossover design may not be practically feasible; therefore, a parallel design can be used.
	Healthy volunteers
	Strength: 120 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics.

	Other design aspects: The use of only one sex, e.g. males only or exactly the same number of male and female subjects in each treatment group, is recommended since sex differences are known to contribute to a high inter-subject variability for lanreotide. C_{max} has been found to be significantly higher in male than in female subjects and the rate of absorption was slower in female subjects.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, C_{τ} (concentration at the end of the dosing interval, i.e. day 28), AUC_{0-168h}, $AUC_{168-672h}$ and AUC_{672h-t}
	90% confidence interval: 80.00–125.00%
Waiver of bioequivalence study	A waiver of in vivo bioequivalence studies may be granted if the test product has the same quantitative composition as the reference product and demonstrates equivalent molecular, structural, and thermodynamic properties as the reference product using a range of orthogonal techniques. These studies could include: • Molecular structure characterisation (peptide sequence): HRMS (High Resolution Mass Spectrometry) and NMR • Molecular scale organisation: FTIR spectroscopy & FT-Raman spectroscopy • Supramolecular scale organisation (peptide folding): Freeze-fracture TEM, Small-Angle X-ray Scattering (SAXS) and Wide Angle X-ray Scattering (WAXS) or similar methods • Thermal stability: temperature-dependent SAXS.

	• Water behaviour: Differential scanning calorimetry (DSC) • Rheological property characterisation: Injectability measurements • In vitro dissolution study At least 5 batches of the test and reference product should be included in the comparability studies. *More batches may be needed in case of higher variability of the reference product results*. The selection of studies, choice of statistical methods and acceptance criteria should be justified.

* 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.