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Committee for Medicinal Products for Human Use (CHMP)

Levodopa/Carbidopa/Entacapone film-coated tablet 200 mg/50 mg/200 mg, 175 mg/43.75 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 100 mg/25 mg/200 mg, 75 mg/18.75 mg/200 mg and 50 mg/12.5 mg/200 mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party	February 2016
Adoption by CHMP for release for consultation	1 April 2016
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End of consultation (deadline for comments)	31 July 2016
Agreed by Pharmacokinetics Working Party	October 2016
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Keywords	***Bioequivalence, generics, levodopa, carbidopa, entacapone***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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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)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Entacapone is considered a low solubility compound.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: a bracketing approach may be applied including at least the highest strength (200 mg/50 mg/200 mg).

	Number of studies: at least two single dose studies (including 200 mg/50 mg/200 mg fasted). **Background:** the number of studies depends on the composition of the applied products.
	Other critical aspects: high intra-subject variability in the pharmacokinetic parameters of entacapone has been reported. A replicate cross-over design study may be considered.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, and C_{max}
	90% confidence interval: 80.00–125.00% for AUC_{0-t} of all substances and for C_{max} of those with low variability (CV_{intra} < 30%). Up to 69.84-143.19% for C_{max} of substances with high variability (CV_{intra} > 30%). **Background:** entacapone may be considered a highly variable drug.

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

** This tentative BCS classification of the drug substance serves to define whether in vivo studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III) the Applicant may choose between two options: in vivo approach or in vitro approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85% within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).