1 1 April 2016
2 EMA/CHMP/162889/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 Levodopa/Carbidopa/Entacapone film-coated tablet 5 200mg/50mg/200mg, 175mg/43.75mg/200mg, 6 150mg/37.5mg/200mg, 125mg/31.25mg/200mg, 7 100mg/25mg/200mg, 75mg/18.75mg/200mg and 8 50mg/12.5mg/200mg product-specific bioequivalence 9 guidance

10 Draft

Draft Agreed by Pharmacokinetics Working Party	February 2016
Adoption by CHMP for release for consultation	1 April 2016
Start of public consultation	2 May 2016
End of consultation (deadline for comments)	31 July 2016

11
12

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu.

13

Keywords	***Bioequivalence, generics, levodopa, carbidopa, entacapone***

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Levodopa/Carbidopa/Entacapone film-coated tablet 200mg/50mg/200mg, 175mg/43.75mg/200mg, 150mg/37.5mg/200mg, 125mg/31.25mg/200mg, 100mg/25mg/200mg, 75mg/18.75mg/200mg and 50mg/12.5mg/200mg 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:** Entacapone is a low solubility compound
BE Study design *in case a BCS biowaiver is not feasible*	**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.
	Number of studies: At least two single dose studies

	Background: The number of studies depends on the composition of the applied products.
	Other critical design aspects: Significant intra-subject variability in the pharmacokinetic parameters of entacapone has been reported. A replicate cross-over design study can be carried out as per the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1; section 4.1.10).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, C_{max}
	90% confidence interval: 80.00– 125.00 % for AUC_{0-t} of all substances, 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 based on CV_{intra} **Background:** Entacapone may be considered a highly variable drug

*Since high intra-individual variability (CVintra > 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).