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Committee for Medicinal Products for Human Use (CHMP)

## Carglumic acid dispersible tablets 200 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party (PKWP)	October 2013
Adoption by CHMP for release for consultation	24 October 2013
Start of public consultation	15 November 2013
End of consultation (deadline for comments)	15 February 2014
Agreed by Pharmacokinetics Working Party	March 2015
Adoption by CHMP	26 March 2015
Date of coming into effect	1 October 2015
Draft revision agreed by Methodology Working Party (MWP)	29 April 2025
Adoption by CHMP	12 May 2025
Date of coming into effect	1 December 2025

\*This revision addresses a change in requirements from a fasted study to either fasted or fed in accordance with the ICH M13A guideline

<b>Keywords</b>	<b><i>Bioequivalence, generics, carglumic acid</i></b>
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# Carglumic acid dispersible tablets 200 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)\*

<b>BCS Classification**</b>	<b>BCS Class:</b> <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> <b>neither of the two</b> <b>Background:</b> Carglumic acid may be considered a low solubility compound.
<b>Bioequivalence study design</b> <i>in case a BCS biowaiver is not feasible or applied</i>	<b>single dose</b> <b>cross-over</b>
	<b>healthy volunteers</b>
	<input type="checkbox"/> <b>fasting</b> <input type="checkbox"/> <b>fed</b> <input type="checkbox"/> <b>both</b> <input checked="" type="checkbox"/> <b>either fasting or fed</b> <b>Background:</b> The SmPC recommends intake (immediately) before meals for pharmacodynamic reasons; therefore, a fed study is acceptable. However, a fasted study is also acceptable as it will be conducted in healthy volunteers.
	<b>Strength:</b> 200 mg <b>Background:</b> 200 mg is the only strength.

	<b>Number of studies:</b> One single dose study.
<b>Analyte</b>	<input checked="" type="checkbox"/> <b>parent</b> <input type="checkbox"/> <b>metabolite</b> <input type="checkbox"/> <b>both</b>
	<input checked="" type="checkbox"/> <b>plasma/serum</b> <input type="checkbox"/> <b>blood</b> <input type="checkbox"/> <b>urine</b>
	<b>Enantioselective analytical method:</b> <input type="checkbox"/> <b>yes</b> <input checked="" type="checkbox"/> <b>no</b>
<b>Bioequivalence assessment</b>	<b>Main pharmacokinetic variables:</b> AUC <sub>0-72h</sub> and C <sub>max</sub>
	<b>90% confidence interval:</b> 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<sub>max</sub>. If high intra-individual variability (CV<sub>intra</sub> > 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 seem 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).