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EMA/CHMP/260596/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments on 'Vortioxetine hydrobromide immediate release tablets 5 mg, 10 mg, 15 mg, and 20 mg; vortioxetine lactate oral drops solution 20 mg/ml product-specific bioequivalence guidance' (EMA/CHMP/474974/2016)

Comments from:

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1. General comments

Stakeholder number (	General comment (if any)	Outcome (if applicable)

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line(s) 22 - 23 Table / BCS classification / Bioequivalence study design / Number of studies		**Comment:** Vortioxetine has been authorized in the EU as film-coated tablets (EU/1/13/891/001-035, 037-040) and oral drops solution (EU/1/13/891/036) containing vortioxetine as hydrobromide and (D, L)-lactate salt, respectively. During the initial marketing authorization procedure (Procedure No. EMEA/H/C/002717; applicant H. Lundbeck A/S), vortioxetine has been categorized by European Medicines Agency (EMA) as a BCS class I drug (high solubility / high permeability) (Assessment report EMA/699150/2013). Based on publicly available solubility data from U.S. Food and Drug Administration (FDA), the highest single dose (vortioxetine hydrobromide equivalent to 20 mg of base) is completely dissolved in 250 mL of buffers within the range of pH 1 – 6.8 (NDA 204-447; Clinical Pharmacology and Biopharmaceutics Review(s)). Vortioxetine (D, L)-lactate has higher solubility in polar solvents as compared to hydrobromide salt (EMA/699150/2013). Therefore, both vortioxetine salts can be considered highly soluble drug substances in line with the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr). In terms of absorption, vortioxetine displayed a complete absorption in humans. The mean recovery of 14C-radioactivity in a mass balance study was 85%, with approximately 59% and 26% of radioactivity excreted in the	**Not agreed**. The statement on BCS classification in the respective EPAR is acknowledged though not agreed and hence not adopted for the PSBGL. The BCS-based biowaiver approach requires clear prerequisites regarding drug substance characteristics which are considered insufficiently met for Vortioxetine hydrobromide and lactate based on currently available data. Vortioxetine hydrobromide: Based on available data (EMA and US-FDA) solubility at pH 6.8 in the recommended aqueous phosphate buffer (50 mM) is 0.078 mg/ml at best, i.e. not reaching the minimum solubility for being 'highly soluble' according to the BCS. Further data indicate even less solubility using 100 mM phosphate buffer. Although these results may be partly considered borderline, 'high solubility' should be unequivocally ensured in order to justify applying the BCS based biowaiver approach. Regarding absorption the US-FDA concluded 'medium permeability' based on 59 % of

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		urine and faeces, respectively. In this study, approximately all radioactivity could be attributed to vortioxetine and identified metabolites (EMA/699150/2013). Additionally, bioequivalence between oral drops solution (20 mg/mL; formulation used for marketing) and the 20 mg film-coated tablet formulation has been proven (EMA/699150/2013). Thus, formulation characteristics do not seem to play a significant role in the absorption. Based on the above studies it can be concluded that vortioxetine is completely absorbed (the extent of absorption ≥85%). In summary, currently available data generated during the initial marketing authorization confirm that vortioxetine belongs to a BCS class I drug (high solubility / high permeability) and thus the draft product-specific bioequivalence guidance should be updated accordingly. **Proposed changes:** (1) Table 'Requirements for bioequivalence demonstration (PKWP)': Section BCS Class, change to: ☒ I ☐ III ☐ Neither of the two, and modify the Background Section to: Vortioxetine hydrobromide / (D, L)-lactate is a high solubility compound with complete absorption. (2) Table 'Requirements for bioequivalence demonstration (PKWP)': Section Bioequivalence study design / Number of studies, the text should be modified to: **Tablets:** one single dose study; **Oral solution:** studies may be waived in line with requirements laid by CPMP/EWP/QWP/1401/98	radioactivity recovered in urine and absolute bioavailability of 75 %. The conclusion is in line with the currently proposed EMA PSBGL, i.e. the compound cannot be considered highly permeable. Vortioxetine lactate: There are no data available substantiating the conclusion of high solubility. Of note, the respective liquid formulation represents an alcoholic solution including Hydroxypropylbetadex as an additional solubilizing excipient. The cited reference for the possibility to waive in vivo studies (CPMP/EWP/QWP/1401/98 Rev.1/Corr** App.II) refers to aqueous oral solutions and hence does not apply. It is acknowledged that formulation characteristics seem to have a rather small impact on bioavailability based on available data indicating bioequivalence of the solid and liquid formulation. However, this seems to be mainly attributed to slow absorption processes and long elimination half-life and does not prove the drug substance to belong to BCS1 or otherwise justify the BCS based biowaiver approach for future generics.

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		Rev.1/Corr (Appendix II) and PKWP Questions & Answers (6.3 Biowaivers).	**Conclusion**: No changes.