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EMA/CHMP/162825/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments on 'Asenapine sublingual tablets 5 and 10 mg product-specific bioequivalence guidance' (EMA/CHMP/PKWP/269533/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

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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 16 (Table)		**Comment:** Asenapine maleate is presented as a low solubility compound in the innovator's approval documentation: • *„According to Biopharmaceutics Classification System (BCS), asenapine maleate is classified as a BCS Class 2 compound (low solubility, high permeability). Asenapine maleate is a white to off-white powder with a solubility of 3.7 mg/mL in water.“* (Saphiris (asenapine) sublingual tablets, NDA 22-117). • *„Asenapine maleate is a white to off-white non hygroscopic powder, slightly soluble in water, sparingly soluble in 0.1 M HCl.“* (Sycrest, EMEA/H/C/001177, Assessment Report) **Proposed change**: Table 'Requirements for bioequivalence demonstration (PKWP)': Section BCS Classification, option 'Neither of two' should be ticked off. Change wording of Background to: Asenapine may be considered a low solubility high permeability compound with limited absorption when administered sublingually.	The solubility data is accepted and has been included in the template. In terms of BCS classification, neither of the two' has been ticked.
Line 16 (Table)		**Comment:** The absolute bioavailability of sublingual asenapine at 5 mg	It is agreed that the solubility data in saliva suggests that non linearity at the 10 mg dose

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		is 35 %. The absolute bioavailability of asenapine when swallowed is low (<2 % with an oral tablet formulation) (Sycrest SmPC). Asenapine pharmacokinetics is non-linear (i.e. less than proportional increase in AUC with increased dose) within the recommended dose range. • *"Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The less than proportional increase of Cmax and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration."* (Sycrest SmPC) • *"The less than proportional increase of Cmax and AUC with SL dose may be attributed to limitations in the absorption capacity from the oral mucosa, so that with higher doses a larger portion of the dose may be swallowed as indicated by the metabolite ratios N-desmethylasenapine/asenapine. Since after oral administration N-desmethylasenapine plasma concentrations are considerably higher, the ratio N-desmethylasenapine/asenapine is expected to increase when part of the sublingual dose is swallowed."* (AusPAR, Saphris, Asenapine, Schering-	could be due in part to solubility. Therefore the requirement has been changed to 2 studies at 5 and 10 mg.

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		Plough Pty Limited PM-2009-03233-3-1, 7 March 2011). Asenapine maleate has aqueous solubility of 3.7 mg/mL and it has a pKa value of 8.6. Its log P values (octanol/water) are 4.9 (neutral species) and 1.4 (protonated species). (AusPAR, Saphris, Asenapine, Schering-Plough Pty Limited PM-2009-03233-3-1, 7 March 2011). Similar physicochemical properties were measured and verified by Bartlett et al. (Bartlett JA et al. Understanding the Oral Mucosal Absorption and Resulting Clinical Pharmacokinetics of Asenapine. AAPS Pharm Sci Tech 2012; 13(4):1110-1115). The solubility of asenapine in saliva, as measured in their study, was 5.4 mg/mL. As around 1 ml saliva is present in the oral cavity, the dose to reach saliva saturation is about 5.4 mg. As also concluded in this paper, after sublingual administration of asenapine, drug rapidly partitions into the mucosal membranes, where it is stored for extended periods and then slowly partitions out of this lipid tissue and into the systemic circulation. The bioavailability of a sublingually administered drug at doses below the saturation solubility (i.e. 5 mg) in the mouth is constant and controlled primarily by a mass transport equilibrium. Once the mass transport equilibrium has been reached, no further drug absorption into the sublingual membranes is expected unless a shift occurs in the mass balance (e.g., sufficient drug is transported from	

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		the mucosal membranes and into the systemic circulation in the relatively short time the drug is in contact with the oral cavity). At this equilibrium point, the remaining dose, which cannot be absorbed into the mucosal tissues, will simply be swallowed over time. At doses above the saturation solubility (i.e. 10 mg), the bioavailability becomes more dependent not only on the distribution equilibrium (distribution coefficient) but also additional variables need to be accounted for, e.g. dissolution of excess drug and re-establishing the distribution equilibrium). Thus conducting BE study on the higher strength may be even more discriminating between formulations. **Proposed change**: Table 'Requirements for bioequivalence demonstration (PKWP)': Section 'BE Study design, in case a BCS biowaiver is not feasible or applied': Strength: change wording to '10 mg and 5 mg' Background: change wording to 'Non-linear pharmacokinetics of asenapine may be attributed to both limited solubility and limitations in the absorption capacity from the oral mucosa following sublingual administration. As per the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), for drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most	

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		cases be established both at the highest strength and at the lowest strength (or a strength in the linear range), i.e. in this situation two bioequivalence studies are needed.'	