Annex II

Scientific conclusions and grounds for positive opinion

Scientific conclusions

Overall summary of the scientific evaluation of Simvastatin Vale and associated names (see Annex I)

The marketing authorisation application for a generic simvastatin oral suspension to be marketed as Simvastatin Vale 20 mg/5 ml and 40 mg/5 ml and indicated in the treatment of hypercholesterolemia and cardiovascular disease prevention was supported by a single bioequivalence study comparing the 20 mg/5 ml oral suspension to the 20 mg immediate release tablet of the reference product. Following potential serious risks to public health raised regarding the evidence of bioequivalence for the higher 40 mg/5 ml strength, a referral under Article 29(4) of Directive 2001/83/EC was triggered, requesting the CHMP to give its opinion on whether Simvastatin is bioequivalent to the reference product.

While the CHMP agreed that there was a deviation from the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), which states that for substances with linear pharmacokinetics, bioequivalence should in general be established with the highest strengths, it considered that this deviation should be considered in light of the available data and therefore assessed the Applicant dossier to determine the clinical relevance of the deviation. The CHMP noted that the proposed formulations are largely identical qualitatively and quantitatively and are manufactured according to the same process. The CHMP also evaluated the *in vitro* dissolution data, noting that both products showed rapid and high dissolution levels at pH 7 and that solubility was therefore unlikely to be a limiting factor. The CHMP considered that the pharmacokinetics of simvastatin are fully linear across the therapeutic dose range, that simvastatin is well absorbed and that no significant differences in absorption between the proposed and the reference product could be identified. Finally, the CHMP considered the bioanalytical method used to be sufficiently validated and in line with the bioequivalence guideline.

Overall, having considering the totality of the available evidence, the CHMP concluded that while a deviation from the current bioequivalence guideline is acknowledged, no potential serious risk to public health was identified, that extrapolation of the demonstrated bioequivalence from the 20 mg/5 ml strength to the 40 mg/5 ml strength is possible and that both strengths of the proposed product can therefore be considered bioequivalent to the reference product. In conclusion, the CHMP was of the opinion that the benefit-risk ratio of Simvastatin Vale and associated names is favourable.

Grounds for positive opinion

Whereas

- the CHMP reviewed the available data submitted by the Applicant
- the CHMP considered that the available data allowed extrapolation of the demonstrated bioequivalence from the 20 mg/5 ml strength to the 40 mg/5 ml strength
- the CHMP considered that both strengths of the proposed product can be considered bioequivalent to the reference product

the CHMP has recommended the granting of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Simvastatin Vale and associated names (see Annex I).