EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 May 2013
EMA/264659/2013

Assessment report for Simvastatin Vale and associated names

Pursuant to Article 29(4) of Directive 2001/83/EC

INN of the active substance: simvastatin

Procedure no: EMEA/H/A-29/1358

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Vale Pharmaceuticals Ltd submitted an application for decentralised procedure for Simvastatin 20 mg/5 ml oral suspension and Simvastatin 40 mg/5 ml oral suspension on 27 May 2011.

The application was submitted to the reference Member State (RMS): UK and the concerned Member States (CMS): AT, DE, DK, EL, ES, FI, FR, IE, IT, NL, NO, PT and SE.

The Decentralised procedure UK/H/4688/01-2/DC started on 7 September 2011.

On day 210, major issues on bioequivalence, remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC by UK on 9/11/12. The CMD(h) 60 Day procedure was initiated on 26 November 2012.

Day 60 of the CMD(h) procedure was on 24 January 2013, and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by the United Kingdom on 30 January 2013. The Netherlands and Spain raised public health objections regarding the data submitted to demonstrate bioequivalence between the proposed product and the reference product.

2. Scientific discussion during the referral procedure

2.1. Introduction

Simvastatin is a lipid-regulating drug indicated in the treatment of hypercholesterolemia and cardiovascular disease prevention. The Applicant submitted a marketing authorisation application through the decentralised procedure for Simvastatin Vale, a generic simvastatin oral suspension to be marketed as two strengths, 20 mg/5 ml and 40 mg/5 ml. The application was based on claims of bioequivalence to the reference product Zocor, available in Europe as 20 mg, 40 mg and 80 mg immediate release tablets. The Applicant carried out a single bioequivalence study to support the approval of both proposed strengths. In the absence of an oral suspension formulation for the reference product, the Applicant compared the 20 mg/5 ml oral suspension to the 20 mg immediate release tablet of the reference product, requesting a biowaiver for the 40 mg/5 ml strength. The CHMP noted that the oral suspension formulation is mainly aimed at patients who cannot swallow tablets. The indications proposed were identical to the approved indications of the reference product.

While the reference member state considered the application to be approvable, the objecting concerned member states (CMSs) raised potential serious risks to public health (PSRPH) regarding the data submitted to demonstrate bioequivalence between the proposed product and the reference product. In particular, it was considered that the study conducted with the 20 mg/5 ml strength was insufficient to provide evidence of bioequivalence for the higher 40 mg/5 ml strength, as the study did not comply with 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, which are the most sensitive to identify a possible difference between formulations, unless the active substance is highly soluble or if there are

safety/tolerability reasons. The objecting CMSs considered that because the proposed formulation differed from the reference formulation, because simvastatin is a lipophilic compound and poorly soluble in water and because the higher dose can be administered without expected safety problems, the most sensitive strength to detect differences between the test and reference formulations should be used, i.e. the 40 mg/5 ml strength. As a result, concerns were also raised regarding the possibility, as described in the proposed SmPC, to use the 20 mg/5 ml strength to administer the higher dose. A referral under Article 29(4) of Directive 2001/83/EC was therefore triggered and the CHMP was requested to give its opinion on whether the proposed product Simvastatin Vale could be considered bioequivalent to the reference product.

2.2. Critical evaluation

The CHMP noted that in addition to the clinical bioequivalence study SC02806, the Applicant also claimed equivalence between the proposed product and the reference product based on quality data and an in vitro comparison of the products. The CHMP agreed that the available data confirmed the bioequivalence between the 20 mg/5 ml oral suspension and the 20 mg tablet and that the issue to be resolved was whether the submitted data can be used to extrapolate bioequivalence between the higher 40 mg/5 ml oral suspension strength and the 40 mg tablet. While the CHMP agreed that simvastatin does not meet the solubility requirements to waive the requirement for bioequivalence testing at the higher strength and although there are no significant safety issues associated with the use of the higher simvastatin dose, the CHMP was of the view that this deviation from the guideline should be considered in light of the available data and therefore assessed the Applicant dossier to determine the clinical relevance of the deviation and whether it constitutes a PSRPH.

The CHMP noted that the supportive bioequivalence study was conducted in 2007, before the current revised guideline was adopted. In accordance with the applicable guidelines at the time, the Applicant had selected the 20 mg/5 ml oral suspension strength in order to provide adequate plasma levels for assay while reducing the risk of possible adverse effects.

Regarding the safety of the proposed product, the CHMP noted that another simvastatin oral suspension product was granted marketing authorisation in 2010 based on the same bioequivalence data as provided for the proposed product under consideration and that no clinical concerns have been identified following the marketing of this product.

The CHMP further noted that the proposed 20 mg/5 ml and 40 mg/5 ml formulations are identical in qualitative composition (apart from flavouring). Quantitatively, the formulations differ in the amount of active substance (0.4% compared to 0.8% w/v), which is compensated by a difference in the amount of the two inactive excipients simeticone emulsion sulphate (0.01% compared to 0.02% w/v) and sodium lauryl sulphate (0.04% compared to 0.08% w/v). The two strengths of the proposed product are manufactured to the same standard, in the same factory using the same methodology and equipment.

The CHMP also evaluated the *in vitro* dissolution data provided by the Applicant, comparing the two strengths of the proposed product to the reference product 20 mg tablet across a range of pH values (pH 1.2, 4.5 and 7). Although simvastatin is unstable at lower pH values, both strengths of the proposed product and the reference product showed rapid and high dissolution levels at pH 7 (> 85% within 15 minutes) and solubility was therefore not considered likely to be a limiting factor.

With regards to pharmacokinetics, the CHMP noted the reference product SmPC as well as the literature which state that the pharmacokinetics of simvastatin are fully linear across the therapeutic dose range and that while absolute bioavailability is low (below 5%) due to extensive first-pass metabolism, simvastatin is described in the reference SmPC as being "well absorbed", with figures ranging from 60% to 80% in the literature. A literature review did not suggest that the absorption of simvastatin is rate-limited by *in vivo* drug dissolution to a clinically significant extent. The CHMP also assessed data showing that the extent of absorption is constant over the dose range of 20 to 80 mg for small particles (20µm mean diameter), but decreases with particle sizes (mean diameter) greater than 30µm and was therefore reassured by the small particle size (90% of particles have a diameter below 20µm) which allows maximum absorption and by the fact that the particle size is well controlled. In addition, despite the concentration differences between the two strengths of the proposed product, the percentage of active substance is low in both cases and the CHMP did therefore not expect the resulting small difference to affect the absorption of the active substance, which is also applicable for the reference product. Any difference between the two strengths is further mitigated by dilution in the gut.

Finally, the CHMP considered that the bioanalytical method used is sufficiently validated to accurately measure the active substance at levels obtained with the 20 mg strength with sufficient sensitivity, as the lower limit of quantification (LLOQ) of the assay is 1/10th of the lowest individual Cmax obtained with the proposed product and 1/30th of the mean Cmax for both the proposed and the reference product, which is in line with the bioequivalence guideline (which requires that the LLOQ should be 1/20th or lower). Therefore, whilst the proposed simvastatin suspension differs from the reference immediate release tablet, the CHMP was confident that differences between the two formulations could be adequately detected, especially as the suspension formulation is largely equivalent to crushed tablets administered in a small volume of liquid as the immediate release tablet will be in the suspended state within 15 minutes.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

Overall, having considering the totality of the available evidence, the CHMP considered it reasonable to assume that the 40 mg/5 ml suspension will behave in a dose-proportional manner to the 20 mg/5ml suspension and that any hypothetical small difference is unlikely to have significant clinical consequences. The CHMP therefore concluded that while the deviation from the current bioequivalence guideline is acknowledged, no potential serious risk to public health was identified. Although the bioequivalence of the higher 40 mg/5 ml strength has not been strictly demonstrated, the CHMP considered that the available data, including the *in vitro* characterisation data for both strengths, allowed extrapolation of the demonstrated bioequivalence from the 20 mg/5 ml strength to the 40 mg/5 ml strength and that both strengths of the proposed product can therefore be considered bioequivalent to the reference product.

2.5. Conclusions and benefit risk assessment

Based on:

- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the benefit/risk ratio of Simvastatin Vale and associated names is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion. The divergent positions are annexed to this report and appended to the Opinion.

Appendix

Divergent positions

Article 29(4) referral of Council Directive 2001/83/EC

Procedure No: EMEA/H/A-29/1358

Simvastatin Vale and associated names (INN: simvastatin)

Divergent statement

Based on the presented bioequivalence evidence in their totality, we are of the following opinion:

Considering that:

- simvastatin oral suspension is a different formulation from the reference simvastatin tablet;
- small differences in manufacturing process and excipients may affect the release rate of simvastatin;
- the drug with the highest content of simvastatin is considered to be the most sensitive to detect differences for this formulation;
- simvastatin is a lipophilic compound and poorly soluble in water;
- simvastatin has a complex absorption (it is partly metabolised in the gut by CYP 3A4 and undergoes extensive first pass metabolism in the liver) and uptake in the liver (in which several transporters are involved, like P-gp and OATP1B1), where it exerts its effect before reaching systemic circulation;
- the higher simvastatin dose can be administered without expected safety problems;
- this procedure was submitted when the Guideline on the Investigation of Bioequivalence [CPMP/EWP/QWP/1401/98, Rev.1/Corr**] was already in force, its requirements should have been followed;

we consider that the biowaiver for the proposed 40 mg/5 ml simvastatin suspension cannot be approved.

CHMP member expressing a divergent opinion:

Pieter Neels (BE)	25 March 2013	Signature: .....
Concepcion Prieto Yerro (ES)	25 March 2013	Signature: .....
Sol Ruiz (ES – co-opted)	25 March 2013	Signature: .....

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CHMP member expressing a divergent opinion:

Karsten Bruins Slot (NO)	25 March 2013	Signature: ……