Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet presented by the European Medicines Agency

Scientific conclusions

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

- **Quality issues**

Variations to the drug product - atorvastatin calcium, small, round film-coated tablets - are comprehensively documented and the amendments proposed regarding the harmonisation are considered acceptable by the CHMP. The proposal for changes to the large, oval tablets is also considered to be acceptable.

- **Efficacy and safety issues**

Clinical particulars

Section 4.1 – Therapeutic Indications

Hypercholesterolemia

The MAH's proposal regarding hypercholesterolaemia indications were mostly supported except for the proposal to include the wording that: *'Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios'. This* was not endorsed by the CHMP due to the fact that low HDL-levels is not accepted as a surrogate marker for cardiovascular disease.

The following wording was agreed by the CHMP:

'Hypercholesterolaemia
'{PRODUCT NAME} is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

{PRODUCT NAME} is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.'

Prevention of cardiovascular disease

The proposed SmPC changes were based on data from the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA), and the Collaborative Atorvastatin Diabetes Study (CARDS). The similarities between the two clinical trials as well as the timing of completion of the studies allowed for a joint review in support of an indication for atorvastatin in the prevention of cardiovascular disease.

The indication proposed by the MAH for the prevention of cardiovascular disease is in line with the wording agreed upon by the CHMP on 20-23 March 2006 (CHMP/76062/2006) during the Article 6(12) referral.

The following wording was agreed by the CHMP:
'Prevention of cardiovascular disease

Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.'

Section 4.2 - Posology and method of administration

No differences are made in dosing recommendations for the treatment of hypercholesterolaemia related to the starting dose regimen and the dose titration in 4 week intervals. For the hypercholesterolaemia indication, the MAH proposes removing the additional text around guidelines. As current guidelines for lipid lowering therapy are subject to constant change, the CHMP agreed that it would not seem to be helpful to fix such an advice in the informative texts.

For the indication relating to the prevention of cardiovascular disease, the dosing information is taken from the MRP SmPC.

Regarding the time of medication intake and meals, the information is taken from the MRP SmPC, where it is recommended that each daily dose is given all at once, and at any time of the day, with or without food.

The following wording was agreed by the CHMP:

'Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving {PRODUCT NAME} and should continue on this diet during treatment with {PRODUCT NAME}.

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

The majority of patients are controlled with {PRODUCT NAME} 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia

Patients should be started with {PRODUCT NAME} 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Prevention of cardiovascular disease

In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines……

Method of administration

{PRODUCT NAME} is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.'

Regarding special populations:

- The information derived from a compassionate use study in the homozygous familial hypercholesterolemia patient population has been moved to section 5.1 as suggested by the CHMP.

- A review of the MAH's clinical trial data did not reveal a muscle safety concern in the renal impairment population and a review of the medical literature suggested that statins can be used safely in patients with chronic kidney disease (CKD). The MAH considered it important that physicians be aware of the potential increased risk in this population and monitor these patients for skeletal muscle effects, and a cross-reference to section 4.4 has been added referring to precautionary information regarding patient history of renal impairment as a potential risk factor for development of rhabdomyolysis and recommending closer monitoring for muscle symptoms.

- The MAH has followed the request by the CHMP to include a recommendation for caution for patients with hepatic impairment in section 4.2, with cross references to sections 4.4 and 5.2 of the harmonised SmPC.

- Paediatric information currently exists in the Member States, and this has been harmonised and included.

The following wording was agreed by the CHMP:

'Renal impairment
No adjustment of dose is required (see section 4.4).

Hepatic impairment
{PRODUCT NAME} should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). {PRODUCT NAME} is contraindicated in patients with active liver disease (see section 4.3).

Use in the elderly
Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric use
Paediatric use should only be carried out by specialists.

Experience in paediatrics is limited to a small number of patients (age 4 - 17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolemia. The recommended starting dose in this population is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Developmental safety data in this population have not been evaluated.'

Information regarding Concomitant treatment with other medications has been included in section 4.5.

Section 4.3 - Contra-indications
Myopathy has not been included in the list of contraindications since no contraindication regarding myopathy was agreed for previous Art 30 procedures for pravastatin, simvastatin and fluvastatin. The CHMP agreed with the MAH's proposal.

A contraindication in patients during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures was included.

Contraindications with regard to drug interactions were not included in this section as it is addressed in section 4.5.

The following wording was agreed by the CHMP:
'{PRODUCT NAME} is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients of this medicinal product

- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal

- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).'

Section 4.4 - Special warnings and precautions for use
The list of clinically relevant CYP3A4-inhibitors or transporter inhibitors has been made more general including inhibitors for which there is no interaction data available but where significant interaction could be assumed, since an increased risk can be expected for all potent CYP3A4 or OATP1B1 inhibitors. Lower starting doses of atorvastatin for potent CYP3A4 inhibitors and lower maximum doses of atorvastatin for both potent and moderate CYP3A4 inhibitors have been recommended as requested by the CHMP. The temporary suspension of atorvastatin during fusidic acid therapy has been included in line with the Type II MRP variation (DE/H/0109/001- 004/II/094). As requested by the CHMP the reference to nefazodone as a concomitant treatment was removed.

Section 4.5- Interaction with other medicinal products and other forms of interaction
For pharmacokinetic interactions, introductory information has been retained in the text, whilst the interaction information as well as the corresponding clinical recommendation such as cut-off values for special dosage recommendations or other recommendations has been included. The four cut-off ranges as proposed by the MAH take into account the dose proportional increase in AUC exposure over the 10-80 mg atorvastatin dose range and the available strengths (10, 20, 40, and 80 mg) of atorvastatin tablets. The MAH has provided satisfactory justification for the proposed atorvastatin dosing recommendations associated with the specific fold-increases of atorvastatin exposure during coadministration with the interacting drugs. Lower starting doses of atorvastatin for potent CYP3A4 inhibitors and lower maximum doses of atorvastatin for both potent and moderate CYP3A4 inhibitors have been recommended as requested by the CHMP.

The information in Section 4.5 (text and table formats) has been rearranged such that drug interactions are now grouped under either "Effect of co-administered drugs on atorvastatin" or "Effect of atorvastatin on co-administered drugs." As requested by the CHMP, the MAH has included mechanistic information and extrapolations.

Section 4.6 - Pregnancy and lactation
The MAH proposes the inclusion of the contraindication in patients during pregnancy, while breast-feeding and in women of childbearing potential not using appropriate contraceptive measures with a cross reference to section 4.3 of the SmPC. The information that rare reports of congenital anomalies have been received following exposure to HMG-CoA reductase inhibitors has been included. There is no evidence to support a particular timeframe by which to discontinue atorvastatin treatment prior to conception. Hence, the MAH has not included this wording in the proposed harmonised SmPC.

Section 4.7 - Effects on ability to drive and use machines
The majority of markets currently have the proposed harmonised wording, which is in line with the SmPC guideline dated September 2009. The harmonized text is identical to the current approved MRP SPC.

Section 4.8 - Undesirable effects
The MAH conducted a review of the pooled data from the 17 completed placebo-controlled clinical trials in the atorvastatin clinical trial database as of June 24, 2008, when the review was initiated. The pooled dataset included a total of 16,066 patients, treated for a median period of 53 weeks. Discontinuation due to adverse reactions occurred in 5.2% of patients on atorvastatin compared to 4.0% of the patients on placebo. Data were reviewed for all doses combined (10-80mg) vs placebo, and adverse events were grouped by categories of organ systems. The adverse events in the database were all mapped to MedDRA dictionary terms. This review identified a number of new adverse events that have been added to the atorvastatin CDS and hence also to the SmPC, as well as some changes to the frequencies of existing adverse events.

The MAH agreed to relocate the specified ADRs to their primary MedDRA SOC as requested by the CHMP. Changes to the wording of certain terms as well as justifications for retaining some others were accepted by the CHMP.

Following agreement of the Statin Class wording by the PhVWP in November 2009, the agreed text has been included. As "insomnia" and "nightmares" have already been included in the SmPC and "memory loss" is found as "amnesia", additional terms were not considered to be necessary by the MAH, in order to fulfill the PhVWP Statin Class wording, and this proposal was accepted by the CHMP. The remaining undesirable effects mentioned in the PhVWP Statin Class wording have also been included.

Section 4.9 – Overdose
The MAH has used the MRP SmPC text as the proposed harmonised SmPC text as the overdose wording across the Member State SmPCs is essentially identical to the current MRP SmPC text.

5. PHARMACOLOGICAL PROPERTIES

Section 5.1 - Pharmacodynamic properties
Summaries of the studies investigating the effect of atorvastatin on Atherosclerosis (REVERSAL study), Acute Coronary Syndrome (MIRACL trial), the Prevention of Cardiovascular Disease (ASCOT-LLA and CARDS trials), Recurrent Stroke (SPARCL study) were included. Information from the compassionate-use study in the homozygous familial hypercholesterolaemia patient population has also been included

in this section. Information on paediatric studies has not been included in this procedure as the Art 29 paediatric referral has no bearing on this Art 30 harmonisation referral. The procedures are independent and no data will be brought into one or the other procedure.

Section 5.2 - Pharmacokinetic properties

The MAH has used the MRP text as the harmonised SmPC including the proposed harmonised wording for special populations such as the elderly, paediatrics, gender differences, patients with renal and hepatic insufficiency and SLOC1B1 polymorphism (and its effects on atorvastatin exposure) have been included. Pharmacokinetic data in the paediatric population are not available.

Section 5.3 - Preclinical safety data

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. In line with the SmPC guidance, dated September 2009, brief and qualitative statement covering the nonclinical safety profile of atorvastatin have been included.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Variations to the drug product - atorvastatin calcium, small, round film-coated tablets - are comprehensively documented and the amendments proposed regarding the harmonisation are considered acceptable by the CHMP.

The main areas of disharmony which were addressed by the MAH related to the indication, posology, special warnings and precaution for use, interaction with other medicinal products, pregnancy and lactation, undesirable effects, pharmacodynamic properties, pharmacokinetic properties and preclinical safety data. The MAH has submitted supporting data and arguments relating to these main areas, which have been assessed and considered acceptable by the CHMP. The resulting harmonised SPC, labelling and package leaflet was agreed by the CHMP.

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Lipitor and associated names (see Annex I).