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 Atacand Plus and associated names (see Annex I)

Atacand Plus contains candesartan cilexetil and hydrochlorothiazide (HCT). Candesartan cilexetil is an angiotensin receptor blocker (ARB). Hydroclorthiazide is a diuretic, reduces the volume of the blood, helping control the blood pressure.

Section 4.1 Therapeutic indications

The approved mutual recognition wording stated *"Essential hypertension, where monotherapy with candesartan cilexetil or hydrochlorothiazide is not sufficient."*

There were some differences in Member States (MSs') summary of product characteristics' (SPCs) in the approved indication: most countries stated '*Essential hypertension*', one mentioned the word '*arterial*' (which was omitted in the final proposal), and one included the word '*adult*' (which was considered in the final proposal). In line with the SPC Guideline (2009), two MSs included "*Treatment of"* followed by the indication. This wording was considered in the proposed harmonised SPC.

The CHMP considered that the benefit/risk balance of candesartan cilexetil/hydrochlorothiazide is positive for the below mentioned indication and the proposed wording was supported and in line with current SPC guideline:

"Treatment of essential hypertension, in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy".

Section 4.2 Posology and Method of Administration

Posology

The CHMP considered the following strengths for Atacand Plus tablets indicated for oral use: 8/12.5 mg, 16/12.5 mg, 32/12.5 mg, and 32/25 mg.

All countries' SPCs for candesartan/HCT 16/12.5 mg or higher strengths included a recommendation on dose titration of candesartan before switching to the fixed dose combination.

An additional sentence was introduced by CHMP to stress the preferable practice to titrate with separate components.

The CHMP endorsed the proposed harmonised wording: "*The recommended dose of Atacand Plus is one tablet once daily. Dose titration with the individual components (candesartan cilexetil and hydrochlorothiazide) is recommended. When clinically appropriate a direct change from monotherapy to Atacand Plus may be considered. Dose titration of candesartan cilexetil is recommended when switching from hydrochlorothiazide monotherapy. Atacand Plus may be administered in patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy or Atacand Plus at lower doses. Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment."*

Special populations

These subheadings in this section of the SPCs were revised in accordance with the SPC Guideline (2009). The sections on use in the elderly, patients with intravascular volume depletion, patients with renal impairment, patients with hepatic impairment and paediatric population were also harmonised.

Method of administration

The information on administration of candesartan/HCT with or without food be located previously in section 4.5 was moved to section 4.2.

Section 4.3 Contraindications

- Pregnancy and lactation

A full contraindication in pregnancy and during lactation was previously included in most SPCs. However, the CHMP/PhVWP report on the use of ACE inhibitors and angiotensin II receptor antagonists (ARBs) during the 1st trimester of pregnancy (EMEA/CHMP/PhVWP/474692/2007) indicates that a contraindication during the first trimester of pregnancy is not justified; the use of AIIRAs in the first trimester of pregnancy is not recommended. The use of AIIRAs in the second and third trimester is contraindicated.

- Other contraindications

The CHMP also agreed with the inclusion of a contraindication in patients with hypersensitivity to the active substances or to any of the excipients, severe renal and hepatic impairment and/or cholestasis, refractory hypokalaemia and hypercalcaemia, and gout.

Section 4.4 Special Warnings and Precautions for Use

Warnings regarding renal impairment, kidney transplantation pregnancy, renal artery stenosis, intravascular volume depletion, anaesthesia and surgery, hepatic impairment, aortic and mitral valve stenosis, primary hyperaldosteronism, electrolyte imbalance, metabolic and endocrine effects, photosensitivity, pregnancy and others were harmonised.

Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Based on the information available in the MS'sSPC, this section was updated. In particular, regarding interactions with potassium sparing diuretics, or other medicinal products that may increase serum potassium levels, other medicinal products that induce torsades de pointes, NSAIDS, colestipol or cholestyramine, nondepolarising skeletal muscle relaxants, calcium supplements or vitamin D, beta-blockers and diazoxide, anticholinergic agents, amantadine, cytotoxic medicinal products, alcohol intake, barbiturates, anaesthetics, antidiabetic medicinal products, pressor amines, iodinated contrast media and cyclosporine, among others.

The sentence on the clinical significant interactions was corrected in line with the previous Atacand harmonisation referral. Furthermore, hydrochlorothiazide was omitted, as Atacand Plus contains hydrochlorothiazide.

Section 4.6 Pregnancy and Lactation

Based on the information provided, the CHMP endorsed the harmonised text for the AIIRA as the standard warning elaborated by the CHMP's PhVWP for all AIIRA: the use of AIIRAs in the first trimester of pregnancy is not recommended; the use of AIIRAs in the second and third trimester is contraindicated.

Section 4.7 Effects on Ability to Drive and Use Machines

Information on effects on ability to drive and use machines was included in all countries with slightly different wording in one SPCs. The CHMP endorsed the harmonised text finding the proposed wording acceptable and in line with that of other ARB or antihypertensive SPCs.

Section 4.8 Undesirable Effects

The brief general safety information from clinical studies on doses up to 16/12.5 mg, including withdrawal figures was the same in most countries. The CHMP endorsed this updated information proposed by the MAH as harmonised text: "*In controlled clinical studies with candesartan cilexetil/hydrochlorothiazide adverse reactions were mild and transient. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil/hydrochlorothiazide (2.3 - 3.3%) and placebo (2.7 - 4.3%)".*

This section was updated in accordance with the SPC Guideline (2009), including all ADRs listed in most countries, as the harmonised text. Cough was added as a very rare ADR to section 4.8 of the SPC, as a result of the PSUR evaluation for candesartan/HCT.

Section 4.9 Overdose

The symptomatic manifestations of overdose and recommendations on management if it occurs were included in this section.

Section 5.1 Pharmacodynamic Properties

This section was shortened and harmonised taking into account the current scientific knowledge and in line with the discussions for other sections of the SPC. In particular, updates on clinical efficacy in elderly hypertensive patients, where results from a trial in elderly patients were included, the pharmacodynamic effects of HCT, and the clinical efficacy of candesartan/HCT in hypertensive patients were considered.

Other sections of the SPC were harmonised accordingly.

Package leaflet and labelling

The changes to the SPC were taken into account in the amendments to the PL and labelling as appropriate.

In conclusion, based on the assessment of the MAH proposal and responses, and following the discussions of the committee, the CHMP adopted the harmonised set of PI for Atacand Plus and associated names. In particular, the indication and its associated posology recommendation, the contraindications and the pregnancy and lactation sections were harmonised.

Based on the above, the CHMP considers the benefit risk ratio of Atacand Plus to be favourable and the harmonised PI to be appropriate.

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

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 Atacand Plus and associated names (see Annex I).