European Medicines Agency

London, 28 May 2009
Doc. Ref. EMEA/CHMP/335293/2009
EMEA/H/A-30/1000

Questions and answers on the referral for Diovan Comp and associated names tablets containing valsartan (80, 160 or 320 mg) and hydrochlorothiazide (12.5 or 25 mg)

The European Medicines Agency (EMEA) has completed a review of Diovan Comp and associated names. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that there is a need to harmonise the prescribing information for Diovan Comp in the European Union (EU) and the European Economic Area (EEA).
The review was carried out under an 'Article 30' referral[1].

What is Diovan Comp?
Diovan Comp contains two active substances, valsartan and hydrochlorothiazide. Valsartan belongs to a class of medicines known as angiotensin II receptor antagonists, which help to control high blood pressure. Angiotensin II is a substance in the body that causes vessels to tighten, thus causing blood pressure to increase. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered. Hydrochlorothiazide is a diuretic. It works by increasing urine output, reducing the amount of fluid in the blood and lowering the blood pressure.
Diovan Comp is used to treat patients with hypertension (high blood pressure), and is also available in the EU under other trade names: Co-Angiosan, Co-Angiosane, Co-Dalzad, Co-Diovan, Co-Diovane, Co-Novasan, Co-Novocard, Cordinate Plus, Corixil, Co-Tareg, Cotareg, Diovan HCT, Kalpress Plus, Levetix, Mitten Plus, Nazzec, Provas Comp, Provas Plus, and Valsartan/Hydroklortiazide. The company that markets these medicines is Novartis.

Why was Diovan Comp reviewed?
Diovan Comp and associated names are authorised in the EU via national procedures. This has led to differences in the way the medicine can be used in the different member states where the medicine is marketed, as reflected in the Summaries of Product Characteristics (SPCs), labelling and package leaflets. Diovan Comp was identified as needing harmonisation by the Co-ordination Group on the Mutual and Decentralised Procedures – Human (CMD(h)).
On 27 May 2008, the European Commission referred the matter to the CHMP in order to harmonise the marketing authorisations for Diovan Comp and associated names in the EU and the EEA.

What are the conclusions of the CHMP?
The CHMP, in the light of the data submitted and the scientific discussion within the Committee, was of the opinion that the SPCs, labelling and package leaflets should be harmonised across the EU.

4.1 Therapeutic indications

The CHMP agreed on a harmonised indication (the disease for which the medicine may be used):
"*Treatment of essential hypertension in adults. Diovan Comp fixed-dose combination is indicated in*

[1] Article 30 of Directive 2001/83/EC as amended, referral on the grounds of divergent decisions adopted by member States

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

patients whose blood pressure is not adequately controlled on valsartan or hydrochlorotiazide monotherapy"
The CHMP discussed the use of Diovan Comp in patients previously treated with other angiotensin II receptor antagonists and agreed that the switch to Diovan Comp should only be for patients previously treated with valsartan. The new wording also means that in all member states Diovan Comp will also be used in patients previously treated with hydrochlorothiazide.

4.2 Posology and method of administration

The CHMP discussed how Diovan Comp, which is a fixed-dose combination of two active substances, should be introduced in to the treatment of patients whose blood pressure is not controlled with either of the active substances used alone. The CHMP recommended wordings for the dosage section giving more precise instructions on how to switch to Diovan Comp. In particular, the CHMP agreed that patients not adequately controlled with valsartan or hydrochlorothiazide can be switched directly to Diovan Comp as long as the new treatment is in line with the recommended dosages for the individual active substances. In addition, before prescribing higher strengths of Diovan Comp, doctors should consider that in most patients maximal effects are observed within four weeks, but in some patients four to eight weeks treatment may be required.

4.3 Contra-indications

The CHMP also agreed on a harmonised wording for the contra-indications (situations where the medicine must not be used):
"- Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
- *Second and third trimester of pregnancy (section 4.4 and 4.6).*
- *Severe hepatic impairment, biliary cirrhosis and cholestasis.*
- *Severe renal impairment (creatinine clearance <30 ml/min), anuria.*
- *Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia."*

The Committee noted that some contra-indications that were included in the SPC in some member states could be removed, as they were now covered by the harmonised wording. The contra-indications removed were: hepatic encephalopathy, biliary obstruction, gout and Addison's disease. The Committee also removed a contraindication for women who are breastfeeding because it considered that the amount of hydrochlorothiazide found in breast milk was very low.

Other changes

The CHMP harmonised the SPC section on special warnings and included warnings about photosensitivity and problems with the function of the parathyroid glands in patients taking 'thiazide' diuretics such as hydrochlorothiazide.
The Committee also harmonised the SPC section on interactions with other medicines. The new wording clarifies the possible interactions with Diovan Comp, and identifies which interactions are linked to each, or to both, active substances.
The amended information to doctors and patients is available here.

The European Commission issued a decision on 26 May 2009.

Rapporteur:	Dr Alar Irs (Estonia)
Co-Rapporteur:	Dr Liv Mathiesen (Norway)
Referral start date:	June 2008
Company responses provided on:	27 October 2008, 16 February 2009
Opinion date:	19 March 2009