European Medicines Agency

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Questions and answers on the referral for Diovan film coated tablets and hard capsules containing valsartan 40, 80, 160 or 320 mg

The European Medicines Agency (EMEA) has completed a review of Diovan (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 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?

Diovan 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. Diovan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

Diovan can be used to treat patients with hypertension (high blood pressure), patients who just have had a heart attack (between 12 hours and 10 days earlier), or patients with heart failure when they show signs that their heart not working fully, such as shortness of breath, and swelling of the feet and legs due to fluid build-up. In heart failure, Diovan is used when other types of medicines used in heart failure such as Angiotensin Converting Enzyme (ACE) inhibitors or beta blockers, cannot be used. It can be used on its own and in combination with ACE inhibitors.
All strengths can be used in these diseases, except the lowest (40 mg) strength, which cannot be used to treat hypertension. The 320 mg strength was not available in all markets.

Diovan can also be available in the EU and the EEA under other trade names: Angiosan, Cordinate, Dalzad, Diovane, Kalpress, Miten, Novacard, Provas, Rixil, Tareg, and Varexan. The company that markets it is Novartis.

Why was Diovan reviewed?

Diovan is authorised in the European Union (EU) via national procedures. This has led to divergences across member states on the way the medicine can be used, as seen in the differences observed in the Summaries of Product Characteristics (SPCs), labelling and package leaflets in the countries where the product is marketed. Diovan has been identified as needing harmonisation by the Co-ordination Group on the Mutual and Decentralised Procedures – Human (CMD(h)).
On 30 May 2008 the European Commission referred the matter to the Committee for Medicinal Products for Human Use (CHMP) in order to harmonise the marketing authorisations for Diovan in the EU and the EEA.

[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

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.

The areas harmonised include:

Therapeutic indications
The CHMP endorsed the use of Diovan in the *"treatment of essential hypertension"***.** The Committee also concluded that the 320 mg dose provides a modest, but statistically significant additional reduction in blood pressure compared to 160 mg and a similarly modest increase in the rate of blood pressure control.

The CHMP also discussed the indications in the treatment of heart failure and after a recent myocardial infarction (MI). The Committee noted that some Member States (MSs) had a limitation of the use of Diovan after MI to patients intolerant to ACE inhibitors. But considering that valsartan given on its own is at least as effective as captopril (an ACE inhibitor) given on its own in the reduction of total mortality after an acute MI, the CHMP endorsed the harmonised indication: *Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours – 10 days) myocardial infarction.*

Posology and method of administration
The CHMP discussed three areas where there was a divergence:

- the use of Diovan with ACE inhibitors and betablockers (triple combination) in chronic heart failure,
- how to manage dose increases,
- dosage recommendations in patients with renal and hepatic impairment.

Looking at the results of studies where triple combination treatment was used (such as a study called VALIANT), the CHMP noted that as there was no increased mortality in patients receiving all three medicines, and therefore there should be no concerns regarding the triple combination. However the Committee agreed that such a combination should still not be recommended until there is more evidence to support its positive benefit-risk balance. In conclusion, the CHMP endorsed the following text:
"The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.
Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see sections 4.4 and 5.1).
Evaluation of patients with heart failure should always include assessment of renal function."

Contraindications
The CHMP noted that there was a divergence on whether the use of Diovan should be contraindicated in patients with kidney failure. Having assessed the data available, the CHMP agreed that valsartan 80 mg can be used as a starting dose in patients with reduced kidney function. The Committee noted that there has been no study of valsartan in patients with severe kidney failure, but they did not identify any possible safety issue has he primary route of elimination of valsartan is via the digestive (biliary), not renal route The CHMP therefore recommended that the contraindication be removed.

However, because Diovan is eliminated via the biliary route, the CHMP agreed that it should be contraindicated in patients with severe liver diseases and "*should not be administered in patients with severe hepatic impairment, cirrhosis or biliary obstruction*".

The CHMP also aligned the contraindication for the use of Diovan during pregnancy or lactation with recent the recommendations of the Pharmacovigilance experts, and therefore recommended that the contraindication in pregnancy be removed and the recommendation for the use during breast feeding be: *"Because no information is available regarding the use of valsartan during breastfeeding, Diovan (Valsartan) is not recommended and alternative treatments with better established safety profiles*

during breast-feeding are preferable, especially while nursing a newborn or preterm infant".

Special precautions

The CHMP considered the need to harmonise a number of precautions for use:

- concomitant use of other medicinal products containing, or raising the level of, potassium. The CHMP endorsed the following text: "*If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised*".
- patients with liver impairment or cholestasis (problems with the elimination of bile).The Committee agreed that no initial dose adjustment is needed in patients with mild to moderate impairment of liver function. However, the dose of valsartan should not exceed 80 mg in patients with cholestasis and should be used with caution. The CHMP endorsed following text:
  No dosage adjustment is required for patients with a creatinine clearance >10ml/min.
  In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg (see section 4.4).

The CHMP also updated other parts of the products information to put it in line with the new data available. The amended information to doctors and patients is available here.

For publication with complete documentation after commission decision:

The European Commission issued a decision on 16 February 2009.

Rapporteur:	Dr Alar Irs (Estonia)
Co-rapporteur:	Dr Liv Mathison (Norway)
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