Annex II

Scientific conclusions

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Background information

Diotop 75 mg / 20 mg is a fixed dose combination product consisting of diclofenac sodium and omeprazole. Each modified release capsule contains 75 mg diclofenac sodium (25 mg as gastro-resistant pellets and 50 mg as prolonged release pellets) and 20 mg of omeprazole (gastro-resistant pellets). The proposed indication is: symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in adult patients at risk of developing NSAID associated gastric and/or duodenal ulcers who are adequately controlled with diclofenac and omeprazole.

The applicant Temmler Pharma GmbH submitted in Germany (DE) an application for a Marketing Authorisation (MA) for Diotop 75 mg / 20 mg modified-release hard capsules, under Article 10b of Directive 2001/83/EC. A decentralised procedure (DCP) with the UK as reference Member State (RMS) and AT, EE, LT, LV and MT as CMSs, concluded positively on 7 November 2016 (UK/H/6135/001/DC). The DCP application was withdrawn from EE, LT, MT and LV during the national phase. This referral procedure concerns the products in UK, AT and DE.

According to Article 10b of Directive 2001/83/EC, new clinical or non-clinical trials relating to the combination (although not the individual active substances) should be submitted. However, according to Notice to Applicants Volume 2A Chapter 1 Section 5.5[1] , a mixed-dossier can be accepted. The applicant has submitted a review of the literature relating to the use of diclofenac and omeprazole in combination. In addition, the applicant refers to relevant clinical guidelines.

The reference member state (RMS) UK considers that the submitted evidence is adequate to support the safety and efficacy profile of Diotop 75 mg / 20 mg. However, the position of DE was that this particular combination of diclofenac/omeprazole in the specific doses 75 mg / 20 mg administered once daily has never been tested in any published study and no new clinical data has been generated. DE considered that extrapolation across different substances, doses and studies is not considered to be an acceptable approach and thus the safety and efficacy of Diotop 75 mg / 20 mg has not been sufficiently shown.

It is noted that the bioequivalence has been demonstrated between the free combination of the recognised reference formulations of the individual mono-components and the proposed fixed combination product and there are no outstanding concerns regarding quality and non-clinical issues.

Overall summary of the scientific evaluation by the CHMP

Diotop 75 mg / 20 mg is intended for symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis in adult patients at risk of developing NSAID associated gastric and/or duodenal ulcers, who are adequately controlled with diclofenac and omeprazole.

Bioequivalence has been demonstrated between Diotop 75 mg / 20 mg and the free combination of the recognised reference formulations of the individual mono-components.

The relevant contribution of omeprazole to the desired therapeutic effect of the product has been demonstrated; the addition of a proton pump inhibitor in patients requiring long-term use of NSAIDs who are at risk of gastroduodenal ulceration has previously been recommended by the CHMP. Moreover, following an Article 30 procedure of Directive 2001/83/EC for Losec and associated names (EMEA/H/A-30/1001), the harmonised indications for omeprazole products include the prevention of NSAID-associated gastric and duodenal ulcers in patients at risk with omeprazole dosed at 20 mg

[1] Notice to Applicants Volume 2A Chapter 1
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/a/vol2a_chap1_201507.pdf

daily. In addition, there are literature data from several large RCTs supporting the safety and efficacy of omeprazole 20 mg daily for the treatment, maintenance and/or prevention of NSAID-associated gastroduodenal ulceration in patients with arthritis.

The 75 mg daily dose of diclofenac is approved for other diclofenac products in the EU for the symptomatic treatment of rheumatic disease. This specific dose is also supported by bibliographical evidence submitted by the applicant. Data from studies of higher doses of diclofenac or other NSAIDs can be extrapolated to support the efficacy and safety of the specific combination. Moreover the mechanisms for both NSAID-associated GI toxicity and the gastro-protective efficacy of omeprazole are not expected to differ across the different non-selective NSAIDs studied, which are all associated with a risk of upper GI complications. CHMP also noted that there is a risk of GI complications with diclofenac 75 mg QD based on epidemiological data.

The CHMP acknowledged that there is no literature data regarding the specific free combination of diclofenac 75 mg QD and omeprazole 20 mg QD. However, the CHMP took into consideration the Guideline on clinical development of fixed combination medicinal products[2] and concluded by consensus that the development of Diotop 75 mg/20 mg is in line with it, since the Guideline does not preclude extrapolation from higher doses and different substances if scientifically justified. Therefore, the CHMP considered that in the context of the harmonised gastro protection indication for omeprazole products in the European Union, the totality of the data presented by the applicant and the well-known safety and efficacy profile of omeprazole and diclofenac, the therapeutic efficacy and the safety of Diotop 75 mg/20 mg is adequately justified. DE is in agreement with the CHMP conclusion.

Based on the review of all available data, the CHMP considers that the benefit-risk balance of Diotop 75 mg / 20 mg modified-release capsules, hard and associated names is favourable and therefore recommends the granting of the marketing authorisation.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC where Germany raised objections as a potential serious risk to public health;
- The Committee considered the totality of the data submitted by the applicant in support of Diotop 75 mg / 20 mg modified-release capsules, hard;
- The Committee considered the (Co-)Rapporteur's assessment report;
- The Committee was of the view that the submitted bibliographical data demonstrate sufficiently the safety and efficacy of the proposed fixed dose combination product.

The Committee, as a consequence, considers that the benefit-risk balance of Diotop 75 mg / 20 mg modified-release capsules, hard and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.