15 November 2018
EMA/813519/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Invented name: Diotop 75 mg / 20 mg modified-release capsules, hard and associated names

INN: diclofenac/omeprazole

Procedure number: EMEA/H/A-29(4)/1474

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background Information

An application was submitted under the mutual recognition procedure for Diotop 75 mg / 20 mg modified-release capsules, hard and associated names on the basis of the marketing authorisation granted by the United Kingdom (UK) on 7 November 2016.

The application under the current wave was submitted to the concerned Member State (CMS): Germany (DE).

The names of this medicinal product currently authorised following previous mutual recognition procedures (MRPs) and the names of the marketing authorisation holders are listed in Annex I of the CHMP opinion.

The mutual recognition procedure UK/H/6135/001/E/001 started on 16 March 2018.

On day 90, major issues on efficacy and safety, raised by DE, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by UK on 14 June 2018. The CMDh 60 day procedure was initiated on 30 July 2018.

Day 60 of the CMDh procedure was on 27 September 2018, and since there could be no agreement the procedure was referred to the CHMP.

On 28 September 2018 the reference member state (RMS) UK therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. DE raised objections on the safety and efficacy of the proposed fixed dose combination (FDC) and considered them to be a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

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 dose is one capsule daily.

Diclofenac inhibits prostaglandin synthesis via inhibition of both COX-1 and COX-2 isoenzymes of the arachidonic acid pathway. Non-steroidal anti-inflammatory drugs (NSAIDs) appear to exert anti-inflammatory, analgesic and antipyretic activity principally through inhibition of the COX-2 isoenzyme. COX-1 inhibition is suggested to be responsible for the NSAIDs' unwanted effects on gastrointestinal mucosa and platelet aggregation.

Omeprazole inhibits the enzyme H^+,K^+-ATPase (the proton pump) by covalent binding to the luminal surface of the parietal cell. This inhibits both basal acid secretion and stimulated acid secretion. Maximal effect is obtained after 4 days of once daily dosing.

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.

2.2. Assessment of the issues raised as a potential serious risk to public health

The issue raised by DE was that the safety and efficacy of the proposed fixed dose combination have not been sufficiently demonstrated. In the Guideline on clinical development of fixed combination medicinal products[2] it is mentioned that each substance must make a relevant contribution to the desired therapeutic effect for the benefit-risk of the combination to be considered positive. The particular combination of diclofenac/omeprazole in the specific doses 75 mg / 20 mg administered once daily has never been tested in any published study. DE considered that the extrapolation across different substances, doses and studies is not considered to be an acceptable approach.

Summary of evidence of gastro-protective action of omeprazole when used in combination with NSAIDs

In patients requiring long-term use of NSAIDs who are at risk of gastroduodenal ulceration, the addition of a proton pump inhibitor is recommended by the CHMP in the context of the review of the key elements for the summaries of product characteristics (SmPC) of non-selective NSAIDs[3]. 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

[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
[2] Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017)
https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-development-fixed-combination-medicinal-products-revision-2_en.pdf
[3] EMEA/CHMP/343456/2005 https://www.ema.europa.eu/documents/other/key-elements-summaries-product-characteristics-non-selective-nsaids-adopted-chmp-during-its-meeting_en.pdf

NSAID-associated gastric and duodenal ulcers in patients at risk with omeprazole dosed at 20 mg daily.

The applicant has provided literature data from several large randomised controlled studies (RCTs) which investigated the efficacy and safety of omeprazole 20 mg daily for the treatment, maintenance and/or prevention of NSAID-associated gastroduodenal ulceration in patients with arthritis [Scandinavian Collaborative Ulcer Recurrence (SCUR)[4], OPPULENT[5], OMNIUM[6] and ASTRONAUT[7] studies] (Table 1).

Table 1: Summary of RCTs investigating gastroprotective efficacy of omeprazole in combination with NSAIDs

Study	NSAIDs used	Treatment	N	Primary endpoint	Outcome
Scandinavian Collaborative Ulcer Recurrence (SCUR) study	Diclofenac, Naproxen, Tenoxicam, Ibuprofen, Ketoprofen, Others	Omeprazole 20 mg QD or placebo	175	Treatment failure (peptic ulcer, >10 erosions, moderate-severe dyspepsia) up to 3 months	Omeprazole: 24.7% Placebo: 50.0% (P=0.0005)
Omeprazole versus Placebo as Prophylaxis of Ulcers and Erosions from NSAID Treatment (OPPULENT) study	Diclofenac, Naproxen, Indomethacin, Others	Omeprazole 20 mg QD or placebo	168	Probability of remaining in remission (no endoscopic peptic ulcer, multiple erosions, or moderate-severe dyspepsia) for 6 months	Omeprazole: 0.78 Placebo: 0.53 (P=0.004)
Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study	Diclofenac, Naproxen, Ketoprofen, Others	Omeprazole 20 mg QD, misoprostol 200 µg BID or placebo	732	Treatment failure (peptic ulcer, >10 erosions, moderate-severe dyspepsia) up to 6 months	Omeprazole: 36.5% Misoprostol: 48.6% (p=0.001 vs omeprazole) Placebo: 67.7% (p<0.0001 vs omeprazole)

[4] Ekström P, Carling L, Wetterhus S, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. *Scand J Gastroenterol*. 1996;31:753–758

[5] Cullen D, Bardhan KD, Eisner M, et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. *Aliment Pharmacol Ther.* 1998;12:135-40

[6] Hawkey CJ, Karrasch JA, Szczepañski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. *N Engl J Med*. 1998;338:727-734

[7] Yeomans ND, Tulassay Z, Juhász L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. *N Engl J Med*. 1998;338:719-726

Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) study	Diclofenac, Naproxen, Indomethacin, Others	Omeprazole 20 mg QD or ranitidine 150 mg BID	432	As OMNIUM	Omeprazole: 26.2% Ranitidine: 37.7%

In the SCUR study, the patients were taking omeprazole with diclofenac, naproxen, tenoxicam, ibuprofen or ketoprofen versus placebo treatment. The primary endpoint was treatment failure for up to 3 months (defined as peptic ulcer, more than 10 erosions or moderate-severe dyspepsia). It was shown that 50% of the patients receiving placebo experienced treatment failure, compared to 24.7% of the patients taking NSAIDs (p=0.0005).

Similarly, the OPPULENT study examined the gastro-protective efficacy of omeprazole when used in combination with diclofenac, naproxen, indomethacin or other NSAIDs versus placebo. The gastro-protective efficacy of omeprazole was confirmed with the patients receiving omeprazole to have 0.78 probability to remain in remission for 6 months (remission defined as no endoscopic peptic ulcer, multiple erosions or moderate-severe dyspepsia) compared to 0.53 probability of patients in the placebo group. (p=0.004).

In the OMNIUM study the population - patients with healed NSAID-associated peptic ulcers, who required continuous treatment with NSAIDs - received either omeprazole 20 mg QD (once daily) or misoprostol 200 µg BID (twice daily) or placebo in combination with diclofenac, naproxen, ketoprofen or others. Treatment failure up to 6 months (defined as peptic ulcer, more than 10 erosions or moderate-severe dyspepsia) was observed in 36.5% in omeprazole group, 48.6% in misoprostol group and 67.7% in the placebo group (p<0.0001 vs omeprazole).

With the same population and endpoints as the OMNIUM study, the ASTRONAUT study confirmed the gastro-protective efficacy of omeprazole (26.2% treatment failure) when used with different NSAIDs versus ranitidine (37.7% treatment failure).

These data provide evidence of the gastro-protective efficacy of omeprazole 20 mg daily and support the harmonised gastro-protection indication of omeprazole. Despite the various NSAIDs that were used in these studies, there was a significant proportion of patients taking diclofenac at daily dose ranges including 75 mg daily (Table 2). However, it is acknowledged that that the results were not analysed according to individual NSAIDs or doses.

Table 2: Proportion of subjects taking diclofenac, and daily dose ranges: ASTRONAUT, OMNIUM and OPPULENT

Diclofenac	ASTRONAUT	OMNIUM	OPPULENT
Number (%)	157 (29)	215 (23)	53 (32)
Daily dose range	50 – 113 mg	50 – 129 mg	50 mg – not reported

Based on an analysis[8] of 3 of the above mentioned studies (OPPULENT, OMNIUM and ASTRONAUT) over 60% of patients were using diclofenac, naproxen, indomethacin or ketoprofen. Relative risks of upper gastrointestinal (GI) complications of 3.3, 4.1, 4.1 and 3.9 have been assigned respectively to diclofenac, naproxen, indomethacin and ketoprofen[9]. Therefore, these NSAIDs are all associated with a risk of upper GI complications.

Summary of evidence for the combination use of omeprazole and diclofenac

In order to support the safety and efficacy of the fixed dose combination, the applicant has provided literature data from 3 RCTs investigating the gastro-protective effect of omeprazole 20 mg daily in free combination with diclofenac 100-150 mg daily.

The largest of these is the CONDOR study[10], a multicentre, double-blind, triple-dummy, parallel group RCT in patients with osteoarthritis or rheumatoid arthritis on regular NSAID treatment, who were at risk of NSAID-associated gastro-duodenal ulceration. A total of 4,484 patients were randomised 1:1 to celecoxib 200 mg BID or diclofenac 75 mg BID and omeprazole 20 mg QD for 6 months. The primary endpoint was a composite of clinically significant events occurring throughout the GI tract such as haemorrhage, obstruction, perforation or clinically significant anaemia of defined GI origin or presumed occult GI origin. Subjects were predominantly women with osteoarthritis who were over 60 years of age. The proportion reaching the primary endpoint was 0.9% (95% CI: 0.5, 1.3) in the celecoxib group and 3.8% (95% CI: 2.9, 4.3) in the diclofenac and omeprazole group ($p<0.0001$). The difference was driven by anaemia, mainly presumed occult cases (0.4% vs 2.4%) or due to gastroduodenal ulcer or erosions (0.2% vs 0.9%). The incidence of clinically relevant complications such as perforation, obstruction or haemorrhage was comparable between treatment arms.

Tkach et al.[11] conducted an RCT including 118 patients with osteoarthritis and rheumatoid arthritis who had taken an once-daily dose of 100 mg diclofenac over one month and were endoscopically confirmed free from ulcers. These patients were randomized to receive omeprazole 20 mg QD and diclofenac 100 mg QD (n=42), rebamipide 100 mg TID and diclofenac 100 mg QD (n=46), or diclofenac 100 mg QD only (n=30). After 4 weeks, peptic ulcers were detected endoscopically in 9.5% of the diclofenac and omeprazole group, 10.9% of the diclofenac and rebamipide group and 26.6% of the diclofenac group.

Labenz et al.[12] conducted a double-blind placebo-controlled RCT in H. pylori positive patients requiring NSAID therapy who had no past or recurrent peptic ulcer. Besides investigating eradication therapy, 155 patients received diclofenac 50 mg twice daily for five weeks together with 20 mg omeprazole, and 171 patients received diclofenac 50 mg twice daily for five weeks together with a placebo. During the study period of 5 weeks the occurrence of peptic ulcers was reported as 0% and 5.8% for the omeprazole and placebo group, respectively. Similar remission rates were observed in the OMNIUM study after four weeks of the healing phase.

[8] Höer A, Gothe H, Schiffhorst G et al. Comparison of the effects of diclofenac or other non-steroidal anti-inflammatory drugs (NSAIDs) and diclofenac or other NSAIDs in combination with proton pump inhibitors (PPI) on hospitalisation due to peptic ulcer disease. *Pharmacoepidemiology and drug safety* 2007;16:854–858

[9] Castellsague J, Riera-Guardia N, Calingaert B et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug Saf. 2012;35:1127-46

[10] Chan FKL, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet.* 2010;376:173-179

[11] Tkach S, Onischuk L, Balabantseva A. Efficacy and Safety of Rebamipide in Prevention of NSAID-Gastropathy. *International Journal of Biomedicine* 2017;7:57-59

[12] Labenz J, Blum AL, bolten WW, et al. Primary prevention of diclofenac associated ulcers and dyspepsia by omeprazole or triple therapy in *Helicobacter pylori* positive patients: a randomised, double blind, placebo controlled, clinical trial. *Gut* 2002;51:329–335

Based on the submitted evidence the CHMP is of the opinion that data from studies of higher doses of diclofenac or other NSAIDs can be extrapolated to support the efficacy and safety of the specific combination of diclofenac 75 mg QD and omeprazole 20 mg QD. The mechanisms for both NSAID-associated GI toxicity and gastro-protective efficacy of omeprazole are not expected to differ across the different non-selective NSAIDs. A risk of gastrointestinal complications is present at low doses of diclofenac based on epidemiological data: relative risk of 2.33 (95% CI 2.02, 2.64) for diclofenac 75 mg daily versus non-use[13].

3. Benefit-risk balance

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 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.

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. Therefore, data from studies of higher doses of diclofenac or other NSAIDs can be extrapolated to support the efficacy and safety of the specific combination.

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.

[13] Odom M, Mladsi DM, Saag KG, et al. Relationship Between Diclofenac Dose and Risk of Gastrointestinal and Cardiovascular Events: Meta-Regression Based on Two Systematic Literature Reviews. *Clin Ther*. 2014;36:906-917

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.

4. Grounds for 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.