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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

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

Diclofenac 50 mg Tablets

Active substance: diclofenac epolamine

Procedure number: EMEA/H/A-29(4)/1434

Note:

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

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Table of contents

1. Background Information

An application was submitted under the decentralised procedure for Diclofenac 50 mg Tablets on 21 October 2014.

The application was submitted to the reference Member State (RMS): United Kingdom and the concerned Member States (CMS): the Czech Republic, France and Slovakia.

The decentralised procedure UK/H/5906/001/DC started on 11 December 2014.

On day 210, major issues on bioequivalence raised by France and Slovakia 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 the United Kingdom on 4 November 2015. The CMDh 60 day procedure was initiated on 07 December 2015.

Day 60 of the CMDh procedure was on 4 February 2016, and as no agreement could be reached the procedure was referred to the CHMP.

On 5 February 2016 the RMS United Kingdom therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. France and Slovakia raised objections based on the variability of Diclofenac epolamine in the fed state and the lack of evidence of bioequivalence, which was considered to be a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

Diclofenac 50 mg Tablets contain diclofenac epolamine, a salt of diclofenac, formed by the combination of diclofenamic acid with the tertiary amine N-(2-hydroxyethyl)-pyrrolidine. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that inhibits prostaglandin synthesis via inhibition of both COX-1 and COX-2 isoenzymes of the arachidonic acid pathway. 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 unwanted effects on gastrointestinal mucosa and platelet aggregation.

The marketing authorisation application (MAA) for Diclofenac (epolamine) 50 mg immediate release tablets was submitted according to Article 10(1) of Directive 2001/83/EC. One study demonstrating the bioequivalence of diclofenac epolamine tablets vs. Flector (diclofenac epolamine) granules for oral solution in healthy volunteers in the fasted state was submitted by the applicant in support of this MAA. Furthermore, comparative dissolution testing at pH 5.5 demonstrated immediate release from test and reference product, which was used to support the comparative rate and extent of absorption *in vivo* in the fed state.

Section 4.2 of the proposed SmPC for Diclofenac (epolamine) 50 mg immediate release tablets is in line with the reference product, and recommends that: *'… tablets should be swallowed whole with a glass of water, preferably during or after meals. In case of acute crisis, it is recommended that the tablets are taken before meals.'*

The RMS was of the view that the fasted state, when solubility is lowest, is the most sensitive state for the demonstration of bioequivalence. In addition, diclofenac epolamine salts are more soluble and permeable than other diclofenac salts at higher pH, and therefore it was argued that a formulation

specific food effect on dissolution of the active ingredient from the dosage form is less likely as compared with other diclofenac salts.

However the objecting member states argued that the effect of food on Cmax may be formulation-dependent in the case of diclofenac, and that from the available evidence the potential difference in bioavailability (Cmax decrease of up to 70%) may reach such a high level so as to compromise the safe and effective use of the drug. Considering this, it was argued that it was necessary to request a fed study in order to rule out any risk of bio-in-equivalence under fed conditions. The potential serious risk to public health (PSRPH) concern was maintained, and the procedure was referred by the RMS to the CMDh.

During the CMDh referral procedure that followed, no consensus could be reached as the objecting EU Member States maintained their objections, which were considered to represent a potential serious risk to public health. The CMDh therefore referred the matter to the CHMP through an Article 29(4) referral procedure.

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

The applicant submitted data from one bioequivalence study of diclofenac epolamine tablets vs. Flector granules for oral solution in healthy volunteers under fasted conditions. This was a single-dose open-label randomised 2x2 crossover study of acceptable design. The pre-defined criteria for bioequivalence were met for both Cmax and AUC:

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1701.41 ± 457.81	1752.54 ± 450.48	2428.96 ± 920.42	0.25 (0.15 – 0.75)
Reference	1683.79 ± 467.54	1711.91 ± 473.64	2607.59 ± 813.66	0.25 (0.15 – 0.50)
***Ratio (90% CI)**	101.03% **(97.97 – 104.18%)**	101.91% **(99.32 – 104.56%)**	90.45% **(82.68 – 98.96%)**	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

The results of the comparative bioavailability study under fasting conditions demonstrate bioequivalence between reference and test products for all pharmacokinetic parameters.

However, no data was submitted to show the food effect between test and reference product to support this application.

Diclofenac epolamine is a BCS Class II substance with low solubility below pH 4.5. Comparative dissolution testing was not conducted at pH 1.2 and 4.0 due to the insolubility of diclofenac at these pH levels. Release from the tablet formulation at pH 6.8 was very rapid and non-discriminatory. Dissolution conditions at pH 5.5 were therefore optimised and deemed to be the most discriminatory for the drug substance. Comparative dissolution profiles at pH 5.5 demonstrated immediate release of

diclofenac epolamine from both test and reference products, and are supportive of a comparative rate and extent of dissolution *in vivo* in the fed state.

Therefore the applicant argued that there is no public health concern if a marketing authorisation was granted for the product Diclofenac DHEP 50 mg tablets, based on the demonstration of bioequivalence in the fasting state and the data outlined above in support of a claim for a biowaiver for an additional study at the fed state.

As requested by the CHMP, the applicant also performed a bibliographic search on the databases Medline and Embase. Thirty two references were considered for further analysis: 18 main original articles and 14 general reviews. No food-effect study was identified with Diclofenac epolamine. Several references were about food interaction on the pharmacokinetics of Diclofenac K, Diclofenac Na and Diclofenac acid, although there is no agreement on the extent to which the diclofenac formulation contributes to the magnitude of the Cmax decrease. In summary this review of literature by the applicant about the magnitude of the food-effect on the rate of absorption with diclofenac immediate release formulations, allowed to conclude that it reached on average, 50% decrease on Cmax and various delays on tmax, without any loss in the amount of systemic exposure. Given the strong evidence of a food effect on the Cmax and Tmax, this effect is concluded to be both drug substance and formulation dependent.

3. Benefit-risk balance

The SmPC recommendation in section 4.2 is that Diclofenac epolamine tablets should be swallowed whole with a glass of water, preferably during or after meals. In case of acute crisis, it is recommended that the tablets are taken before meals.

The results of the bioequivalence study under fasting conditions demonstrate bioequivalence between reference and test products for all pharmacokinetic parameters. However there is no study/data to show the food effect between test and reference product to support this marketing authorisation application.

The applicant conducted a review of the literature, in response to the question posed by CHMP. There was no literature data regarding diclofenac epolamine formulations. For the sodium and potassium salt, and the acid, a food effect is evident in most studies. The mean Cmax reduction observed with food ranges from 21% to 69%. Limited within study comparisons are available. According to Desjardins et al (2015)[1], there was 60% decrease in Cmax for a diclofenac acid capsule, compared to a 43% decrease in Cmax for a potassium tablet, in the fed state vs fasted. Chen et al (2015)[2] reported a 69% reduction in Cmax for a buffered potassium solution vs a 28% reduction for a potassium tablet, in the fed state vs. fasted state. However in the Chen et al study, the AUC of the solution was greater than that of the tablet in the fasted state.

The CHMP agreed with the applicant that the food effect on Cmax of diclofenac is both drug substance and formulation dependent, based on the review of the literature, which includes potassium and sodium salts, and the acid.

The advice of PKWP was also sought during this procedure. In summary, the view of the PKWP was that under fed conditions the Cmax is highly variable; Cmax ratio fed/fasted ranged from 26-73% for the different formulations, and formulations that are bioequivalent in the fasted state may not be

[1] Desjardins PJ, Olugemo K, Solorio D, Young CL. Pharmaocokinetic propertiesand tolerability of low-dose SoluMatrix diclofenac. Clin Ther, 2015, 37(2), 448-461.
[2] Chen C, Bujanover S, Kareht S, Rapoport AM. Differential pharmacokinetics of diclofenac sodium for oral solution vs immediate-release tablets from a randomised trial: effect of fed and fasting conditions. Headache, 2015, 555, 265-275.

bioequivalent in the fed state, especially if the dosage form is different. Therefore as Diclofenac epolamine tablets and the reference product diclofenac epolamine granules for solution are different oral pharmaceutical formulations, and because literature data show that the food effect on Cmax of diclofenac is not only dependent on the drug substance but also on the formulation, in this case, bioequivalence can only be concluded if bioequivalence is shown under fed as well as fasted conditions. The CHMP endorsed the PKWP's advice.

During the CHMP meeting the applicant presented their view in an oral explanation. A summary of the bioequivalence study in the fasted state was presented as well as a review of the literature submitted. Although it was argued by the applicant that a failure of bioequivalence under fasting state is predictive of a failure of bioequivalence under fed state based on the submitted literature, the CHMP was of the view that the reverse argument could not be upheld i.e that bioequivalence under fasting state is predictive of bioequivalence under fed state, without any evidence to support it.

Therefore the CHMP is of the opinion that the bioequivalence of Diclofenac epolamine tablets and the reference product diclofenac epolamine granules for solution has not been demonstrated for this Article 10(1) marketing authorisation application, since bioequivalence cannot be concluded in the absence of a bioequivalence study in the fed state. Therefore, the CHMP is of the view that the benefit-risk is negative.

4. Risk management

In view of the negative benefit-risk balance, the CHMP did not require the applicant to submit a risk management plan.

5. Grounds for Opinion

Whereas

- The Committee considered the notification of the referral triggered by the United Kingdom under Article 29(4) of Directive 2001/83/EC where France and the Slovakia raised objections that were considered to be a potential serious risk to public health;
- The Committee reviewed the data submitted by the applicant in support of this particular medicinal product Diclofenac (Altergon) 50mg tablets*;*
- The Committee was of the view that in this case bioequivalence of Diclofenac 50 mg tablets vs. the reference product Flector granules for oral solution should be demonstrated in fed conditions as well, in view of the available literature demonstrating that the Cmax of different formulations of diclofenac is affected differently in fed conditions;
- The Committee therefore concluded that there was a lack of appropriate data to support the positive benefit-risk of this medicinal product, Diclofenac (Altergon) 50mg tablets.

The Committee, as a consequence, considers that the benefit-risk balance of Diclofenac is not favourable.

Therefore, the Committee recommends the refusal of the marketing authorisation of Diclofenac (Altergon) in the reference and concerned Member States.