Annex II

Scientific conclusions

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The original application in 2000 under Article 4.8 (a) (II) of Directive 65/65/EEC - bibliographic for new pharmaceutical form and strength, was supported with published literature on efficacy of topical diclofenac as well as data from pharmacokinetics and a clinical study (9702 SUV) of the proposed 4% cutaneous spray formulation.

MIKA Pharma GmbH requested that the marketing authorisation for Diclofenac Sodium Spray Gel 4% granted by the UK in 2001, and subsequently granted by Austria, Estonia, Hungary, Ireland, Latvia, Lithuania and Slovenia, be also recognised in Germany, Italy and Spain as part of a "second wave" Mutual recognition procedure (MRP).

The application subject to this referral therefore concerns a repeat-use mutual recognition procedure (UK-H-0563-001-E-002) for Diclofenac sodium 4% cutaneous spray, solution (PL 18017/0006) with UK as RMS and which involves Italy, Spain, Germany as Concerned Member States.

Day 60 of the CMDh procedure was on 29 March 2018, and since two Member States raised concerns regarding potential serious risk to public health (PSRPH) related to lack of efficacy for the specific 4% spraygel product and inadequate bridging to literature, in particular with other topical diclofenac formulations (including Voltarol Emulgel) for which it was acknowledged that there was adequate evidence of efficacy and safety, the Reference Member State (UK) triggered on 5 April 2018 a referral under Article 29(4) of Directive 2001/83/EC, requesting the CHMP to assess the impact of the objections raised that constitute a potential serious risk to public health.

The applicant's submissions as part of the referral procedure incorporates literature data and discussions on Quality, Clinical Pharmacology, Clinical Efficacy and Clinical Safety aspects.

Quality

The qualitative comparison is based on composition, degree of ionization and complete solubility of active substance. Although the strength of the proposed cutaneous spray is 4% as compared to the Emulgel which is 1% or 2%, this difference in the cutaneous spray was designed to deliver a similar amount of diclofenac to local tissues as the Emulgel.

Clinical Pharmacology

The plasma and tissue pharmacokinetic (PK) data of SprayGel in healthy volunteers, and patients with acute inflammation, are compared to those of Voltaren Sodium Gel and Voltaren Emulgel. Most of the data are cross-study comparisons which are affected by different doses and methods and so no robust conclusions can be drawn from these cross-study comparisons. Nevertheless, it is consistently seen across studies that measurable levels of diclofenac have been reported after application of the spraygel both in systemic exposure and topical exposure (subcutaneous tissue and muscle tissue) at the site of action. The only intra-study comparative data that is available is from study Martin et al. 1997 which indicated that the systemic absorption is comparable for Spraygel and Emulgel, but a conclusion on equivalence - and clinical relevance of systemic absorption - cannot be drawn. Numerically, the exposure of Spraygel is lower than Emulgel and its impact on efficacy cannot be ascertained accurately. However, the systemic exposure is low enough that the adverse event profile seen with oral or other systemically administered NSAIDs is not problematic.

Clinical Efficacy

The applicant included a review of the Predel 2013 study [previously pre-publication known as Study 9702SUV] on the efficacy of Spraygel in acute ankle injury. The defined primary endpoint response, expressed as a decrease in swelling of at least 50% during 10 days of treatment for the 'Full Analysis Set' (FAS), was reached in 87/97 patients treated with diclofenac spray gel (89.7%) compared to

74/94 treated with placebo (78.7%); p = 0.0292 (one-tail) and p = 0.0467 (two-tail). The study was designed and powered to demonstrate superiority with a significant level of 5% one-sided, but the current requirement is now that a significance level of 2.5% one-sided, which the study could not reach.

An effect was seen on the critical secondary endpoint of spontaneous pain visual analogue scale (VAS). The difference in median VAS score was 8 mm at day 3-4 and 4.6mm at day 7-8. Particularly the endpoint of main interest which is pain. However, this study cannot be considered to provide confirmatory evidence on efficacy of Spraygel as the primary endpoint is not validated and statistical analysis does not meet regulatory requirements. However, the study can be considered supportive of efficacy to infer that Spraygel has beneficial activity in the context of this bibliographic application.

The applicant has also reviewed the available published clinical trial literature on topical diclofenac which includes a study on effects of Emulgel on Joint Pain (Predel 2012), study on DHEP (Diclofenac hydroxyethylpyrrolidine plaster), Heparin plaster or placebo plaster (Constantino C et al. 2011) and an uncontrolled study on DHEP gel. All these studies provide evidence on modest efficacy for authorised topical diclofenac formulations of which the most robust is study Predel 2012 with Emulgel,. Further as the systemic and topical exposure data of Emulgel is available for comparison to Spraygel, the Marketing Authorisation Holder bridged the efficacy of Emulgel to Spraygel based on a cross-study comparison of the efficacy endpoints, which are however confounded by differences in study methods and populations. Nevertheless, while it is acknowledged that the efficacy of Emulgel cannot be directly attributed to Diclofenac Sodium Spray Gel 4 %, it is also reasonable to infer that Diclofenac Sodium Spray Gel 4 % has a beneficial effect based on the supportive Predel 2013 study, PK comparisons and cross-study comparisons in a similar range as seen for other topical diclofenac products.

Clinical Safety

The CHMP agreed that topical NSAIDs, including Diclofenac Sodium Spray Gel 4 %, have a proven safety record over many more than 10 years, which is supported by their low systemic bioavailability compared to e.g. oral pharmaceutical forms. In particular their use and substitution for oral and other systemically administered NSAIDS makes a major contribution to patient well-being in view of the available safety data, which supports a markedly lower risk of potentially serious adverse events compared to systemically administered diclofenac containing products.

Overall summary of the scientific evaluation by the CHMP

In summary, when taken together the totality of scientific evidence supports that Diclofenac Sodium Spray Gel 4 % has an acceptable safety and efficacy profile. Therefore the CHMP agreed by majority, that the benefit-risk balance of Diclofenac Sodium Spray Gel 4 % is favourable.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC,
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as a potential serious risk to public health. The Committee considered the available data submitted in support of the use of Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution and associated names , which included a comparison of quality aspects in relation

to authorised topical diclofenac products, and literature covering pharmacokinetic (local and systemic) as well as efficacy and safety data.

- The Committee was of the view that the totality of data submitted justified the efficacy of the applied medicinal product as well as the bridging to the literature, in particular to existing data on topical diclofenac formulations including Voltarol Emulgel formulations.

The Committee, as a consequence, considers that the benefit-risk balance of Diclofenac Sodium Spray Gel 4 % Cutaneous Spray, Solution 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.