ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE MAINTENANCE OF THE MARKETING AUTHORISATIONS SUBJECT TO CONDITIONS AND THE AMENDMENTS OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING KETOPROFEN FOR TOPICAL USE (see Annex I)

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the family of propionics derived from arylcarboxylic acid with analgesic and antipyreticc effects.

Ketoprofen is used for its antipyretic, analgesic, and anti-inflammatory properties by inhibiting cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes reversibly, which decreases the production of pro-inflammatory prostaglandin precursors.

Medicinal products containing ketoprofen for topical use are widely used, including as self-medication, in the treatment of minor pathologies. Ketoprofen topical is generally prescribed for the symptomatic treatment of minor trauma (sprains, bruising), superficial tendonitis, small joint osteoarthritis, acute lumbar pain, and post-sclerotherapeutic phlebitis in case of intense inflammatory reaction.

Ketoprofen is available under the following formulations for topical use: gel, cutaneous spray, cream, plaster, cutaneous foam and cutaneous solution. After topical application, ketoprofen is absorbed slowly through the skin and does not significantly accumulate in the organism.

Medicinal products containing ketoprofen for topical use are authorised in all EEA Member States except for the Netherlands under various brand names and as generics (see Annex I for the list of ketoprofen containing medicinal products for topical use authorised in the EU).

On 9 December 2009, the French Competent Authority (Afssaps) issued a Rapid Alert informing the Members States, the European Medicines Agency and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of its decision to suspend the marketing authorisations of all ketoprofen containing medicinal products for topical use in France due to the conclusions of a national benefit/risk assessment conducted in the period from 2001 to 2009 showing a stabilised incidence of photoallergy despite all Risk Minimisation Measures (RMM) implemented nationally and the apparition of a new element worsening the safety profile of ketoprofen gels (co-sensitisation with octocrylene, a chemical sun filter belonging to the cinnamate family included in several cosmetic and hygiene products).

Before the benefit risk reassessment was performed in France, two national pharmacovigilance (PV) surveys were conducted in this Member State.
The CHMP considered the matter in accordance with Article 107(2) of Directive 2001/83/EC, as amended during the December 2009, January, May and July 2010 CHMP plenary meetings.

Safety

Topical ketoprofen is widely used throughout Europe. There is an identified risk of photoallergy in the scientific literature since 1983. The first case reports originated in the Mediterranean countries were later followed by cases in more northern European areas and from other non-EU countries. In parallel with the increased use of topical ketoprofen, there are accumulating reports of adverse skin reactions (Bagheri et al. 2000). Most of the adverse effects of ketoprofen have been attributed to its photoallergic potential. Skin photosensitivity includes two types of reactions: phototoxicity and photoallergy. Although phototoxicity is not related to the immune response, photoallergy is. The photoallergy is considered to be uncommon, but its exact incidence is unknown.

Since launch, the safety of ketoprofen containing medicinal products for topical use and particularly the related cutaneous risk was put under close monitoring due to the occurrence of serious photoallergy reactions in several Member States. Ketoprofen for topical use was the subject of 2 national surveys in France:

- Pharmacovigilance survey on cutaneous effects covering the period from 1 March 1993 to 31 August 1995
- Extension of the first survey covering the period from 31 august 1995 to 3 august 1996.
- Pharmacovigilance survey conducted over the period from 1 September 1996 to 31 August 2000

The 2 national surveys led to the implementation at national level of many RMMs such as Summary of Product Characteristics (SPC) and Package Leaflet (PL) modifications, Direct Healthcare Professional Communication (DHPC), warning box, and addition of a pictogram on the packaging. However the reporting of photosensitivity reactions persisted despite these extensive RMMs, leading to a benefit/risk ratio reassessment in France. The safety data submitted by the brand leader in France for the reassessment period (namely from 1st January 2001 to 31st January 2009) reported 371 cases (corresponding to 467 AEs). 229 cases were considered as serious. Among the 467 AEs, 386 belong to the SOC "Skin and subcutaneous disorders" and 257 of these (67%) were serious. Photoallergy was the most frequent cutaneous AE and represents 44% of the serious cutaneous reactions. In addition, the safety data showed that photoallergic contact dermatitis from ketoprofen therapy can appear even if it's hazy. This adverse reaction, even if rare, was serious in most cases, leading to hospitalisation and work interruption.
Moreover, during this benefit risk reassessment, a new risk of co-sensitisation with octocrylene was identified. Octocrylene is a chemical sun filter belonging to the cinnamate family included in several cosmetic and care products such as shampoo, after-shave, shower- and bath-gels, skin creams, lipsticks, anti-ageing creams, make-up removers, hair sprays in order to delay photodegradation.

Based on provided data, and as recognised by MAHs themselves, the CHMP concluded that there is a risk of photosensitivity reactions with the use of topical ketoprofen formulations, in particular a risk of photoallergy reactions.

The CHMP also notes that the photosensitivity cases under topic ketoprofen therapy appear following photodegradation of ketoprofen itself by UV radiations, even in case of hazy sun. This adverse reaction is rare and may be serious in some cases leading to hospitalisation, work interruption, and permanent immunisation due to the immunological mechanism of photoallergy.

Some Member States implemented RMMs such as SPC and PL modifications (sections 4.3, 4.4, 4.8), pictogram on the outer package and tube, DHPCs, Press Releases and changes to prescription status. The effectiveness of these RMMs was reviewed in some countries and the conclusions on the efficiency of such measures vary from one Member State to another. For instance, in France, the National Competent Authority concluded that there is a persistence of photosensitivity reactions for years, despite of measures implemented at national level. On the reverse, other Competent Authorities supports the MAHs' position stating that the RMM taken are successful. However the CHMP noted that in the majority of the Member States RMMs have not been applied consistently and therefore no similar data on the effectiveness of such measures was available.

Some MAHs providing answers to the CHMP Lists of Questions or attending the CHMP oral explanations were of the opinion that the RMMs taken were effective across Europe and be wiling to implement additional ones.

Based on the assessed data, the CHMP concluded that there is also a risk of associated-reaction appearing with octocrylene.
The MAHs are of the opinion that the incidence of such a co-sensitization is unknown and expected to be low as per the number of reports available in the public domain (Foti C., 2008; Bennassar A., 2009) to date; therefore the MAHs did not propose any measure to address this concern. The Committee does not support the MAHs' position and therefore is of the opinion that it is necessary to address this concern through RMMs in particular by the introduction of a warning into the SPC.

Based on the above mentioned data, the CHMP recommends RMMs and conditions to the Marketing Authorisations for ketoprofen containing medicinal products for topical use to address the safety issues of photosensitivity including photoallergy reactions and the risk of co-sensitisation with octocrylene.

Therefore, in that respect, the CHMP is of the opinion that some further risk minimisation measures, harmonised across Europe, should be put into place, as follows:

- Routine risk minimization activities: ***Change of the SPC, labelling and PIL***

a. Section Contraindications of the SPC should contain the following:
   i. history of any photosensitivity reaction
   ii. known hypersensitivity reactions, such as symptoms of asthma, allergic rhinitis to ketoprofen, fenofibrate, tiaprofenic acid, acetylsalicylic acid, or to other NSAID
   iii. history of skin allergy to ketoprofen, tiaprofenic acid, fenofibrate or UV blocker or parfumes
   iv. sun exposure, even in case of hazy sun, including UV light from solarium, during the treatment and 2 weeks after its discontinuation

b. Section Warnings and Precautions of the SPC should contain the following:
   i. Hands should be washed thoroughly after each application of the product.
   ii. Treatment should be discontinued immediately upon development of any skin reaction including cutaneous reactions after co-application of octocrylene containing products
   iii. It is recommended to protect treated areas by wearing clothing during all the application of the product and two weeks following its discontinuation to avoid the risk of photosensitisation.
c. Section Undesirable effects of the SPC should contain the following:
   i. Local skin reactions such as erythema, pruritis and burning sensations.
   ii. Cases of more severe reactions such as bullous or phlyctenular eczema which may spread or become generalized have occurred rarely.
   iii. Hypersensitivity reactions.
   iv. Dermatological: photosensitisation
d. Introduction of a pictogram on the outer box and on the immediate packaging
e. Introduction of a warning on the outer box and on the immediate packaging
   i. Do not expose treated areas to sunlight (even hazy) including UV from solarium during the treatment and the 2 weeks after its discontinuation
f. The PIL should be amended according to the above SPC changes (see Annex III).

- Conditions to the Marketing Authorisations:

a. Legal status: Article 71 (1) of Directive 2001/83/EC, states that products likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision shall be subject to medical prescription. The CHMP is of the opinion that it is necessary to limit the treatment only to those patients who really need this therapy and therefore to enable to inform the patients about the proper use of this medicine by Health Care Professionals. This can only be achieved by prescription status. Therefore the CHMP recommends that ketoprofen containing medicinal products for topical use shall be subject to medical prescription as part of the conditions to the MAs.
b. Additional risk minimization activities:
   i. Regular communications (to be repeated twice a year); DHPC reporting the risk for photosensitivity including photoallergic reactions to be sent to physicians including dermatologists, general practitioners (GPs), rheumatologists, pharmacists and physiotherapists
   ii. Pharmacists involvement: educational material to be provided to the patients when topical ketoprofen formulations is dispensed by the pharmacist;
   iii. Target comunications regarding the risks for photosensitivity reactions including photoallergic reactions associated with topical ketoprofen (e.g. Learned Societies' websites, HCP magazines);
   iv. Checklist to be used by the prescribers for assessing comprehension, knowledge, attitudes, and/or desired safety behaviours about the risks (e.g exposure to the sun, washing hands, etc);
   v. Information directly targeted to the patient (regular press release on National Competent Authorities' (NCAs) websites)

The MAHs should implement the educational program for Healthcare Professionals that should be in accordance with the other RMM. The draft outlines of such programme will be submitted to the National Competent Authorities by the MAHs four weeks after notification of the Commission Decision. The complete programme will be agreed with the National Competent Authorities.

The CHMP is of the opinion that measurements of the effectiveness of the above mentioned risk minimizations activities as well as a post authorisation safety study should be part of the conditions to the Marketing Authorisations, as follows:

- The MAHs should submit PSURs with a yearly periodicity. These PSURs should include a specific overview and analysis of the photosensitivity reactions including photoallergy reactions. These reactions should be presented cumulatively and for the period covered by the PSUR. Particular attention should be given to indication, dosage, time to onset, sun exposure and duration of treatment. The yearly PSUR should be submitted to the NCAs, for assessment.
- In addition the MAHs are required within 3 years of the Commission Decision to submit to the CHMP a cumulative analysis of photosensitivity reactions including photoallergy reactions together with a report of the effectiveness of RMMs to be implemented following the Commission Decision.
- The MAHs should perform a *Surveillance study of photocontact dermatitis leading to hospitalization in Europe with a special focus on topical ketoprofen and other topical NSAIDs* to

clarify the incidence of severe photosensitivity reactions associated with topical medications leading to hospitalisation in different geographic areas in Europe, to evaluate possible sequelae, and to assess the impact of risk minimisation strategies. The draft protocol should be submitted for review by the CHMP by 1st December 2010. The timelines for the study conduct and final report should be provided with the draft protocol for agreement by the CHMP. Regular updates on the progress of the study should be provided to the CHMP on a yearly basis.

- A DHPC should be sent following adoption of the CHMP Opinion as per the agreed communication plan.

Efficacy

With regards to efficacy of ketoprofen, the MAHs referred to publicly available data (Patel RK et al 1996, Esparza et al 2007, Moore et al. 1998, Mason et al. 2004) assessing the relative efficacy of topical ketoprofen versus other topical NSAIDs. Upon review of these scientific publications, the CHMP noted that ketoprofen is the only topical NSAID approved in acute low back pain indication. The Committee is of the opinion that there is insufficient direct data allowing conclusions on the relative efficacy of individual NSAIDs in topical preparations.

Benefit/risk

In view of the above data, the CHMP concluded that there is a risk of photosensitivity in particular photoallergy reactions and therefore RMMs should be implemented. The aim of the RMMs to be enforced is to ensure the safe use of topical ketoprofen in strict accordance with the proposed Product Information, Labelling and Package Leaflet by reducing photosensitivity in particular photoallergy reactions. The additional restrictions include a prescription only status, the communication, educational materials (information activities for prescribers, pharmacists, physiotherapists and patients) and a DHPC. The effectiveness of the RMMs will be reviewed by the CHMP in 3 years time.

Ketoprofen is used to relief the patients from pain in minor traumatology (sprains, bruising) and rheumatology conditions, superficial tendonitis, small joint osteoarthritis, acute lumbar pain, and post-sclerotherapeutic phlebitis in case of intense inflammatory reaction. Concerning the efficacy, the MAHs, in their responses, consider that there is consistent significant analgesic and anti-inflammatory clinical effects in patients using topical ketoprofen formulations.

The CHMP concluded that the risk of photosensitivity reactions including photoallergy reactions associated with ketoprofen exists but that the benefit outweights the risk and that the overall risk benefit/balance remains positive.

Overall, the benefit-risk profile of ketoprofen-containing medicinal products for topical use remains favourable and the Marketing Authorisations for products containing ketoprofen for topical use should be maintained subject to amendments to the Product Information and conditions to the Marketing Authorisations.

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE MAINTENANCE OF THE MARKETING AUTHORISATIONS SUBJECT TO CONDITIONS AND THE AMENDMENTS OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The Committee considered the data from the 2 French pharmacovigilance surveys, the French benefit risk reassessment, the MAHs responses to the CHMP questions and the discussions within the Committee,

Whereas,

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing ketoprofen for topical use.
- The Committee considered all the available data submitted on the safety of the ketoprofen containing products.
- The Committee concluded, after having reviewed the available data that under normal conditions of use topical topical ketoprofen is associated with the risk of photosensitivity including photoallergy reactions which can be serious.
- The CHMP also concluded that there is a rare incidence of co-sensitisation with octocrylene.
- The Committee concludes that further risk minimisation measures are needed aiming to limit the risk of photosensitivity reactions including photoallergy reactions.
- The CHMP concluded that the Product Information of all topical ketoprofen-containing products for topical use should include safety information to address the above concerns and therefore recommended amendments to the relevant sections of the Summary of Product Characteristics, Labelling and Package Leaflet. Furthermore, additional risk minimisation measures of these products should also be implemented.
- The Committee, in view of the above findings, concluded that the benefit/risk balance of ketoprofen containing medicinal products remains favourable under the normal conditions of use.

The CHMP has recommended the maintenance of the Marketing Authorisations for all medicinal products referred to in Annex I of the Opinion and to amend the relevant sections of the Summary of Product Characteristics, Labelling and Package Leaflet of topical formulations of ketoprofen, as set out in Annex III of the Opinion. Conditions of the Marketing Authorisations are identified in Annex IV of this Opinion.