



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

29 November 2010  
EMA/824183/2011

## Assessment report for KETOPROFEN containing medicinal products (topical formulations)

International Non-proprietary Name: Ketoprofen

Procedure No. EMEA/H/A-107/1259

Procedure under Article 107 of Directive 2001/83/EC, as amended

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



**TABLE OF CONTENTS**

Page

**1. BACKGROUND INFORMATION ON THE PROCEDURE..... 3**  
1.1. Referral of the matter to the CHMP ..... 3

**2. SCIENTIFIC DISCUSSION ..... 3**  
2.1. Introduction ..... 3  
2.2. Clinical Safety..... 4  
2.2.1. Definition of Photoallergy..... 4  
2.2.2. Safety Data ..... 6  
2.2.3. Discussion..... 9  
2.3. Clinical Efficacy ..... 11  
2.4. Benefit Risk Assessment..... 11  
2.5. Communication plan ..... 12  
2.6. Changes to Product Information ..... 12  
2.7. Conditions to the Marketing Authorisations ..... 14

**3. OVERALL CONCLUSION..... 15**

**4. ANNEXES ..... 15**

# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1. Referral of the matter to the CHMP

On 10 December 2009, France informed the European Medicines Agency of their intention to suspend the marketing authorisations for Ketoprofen topical formulations in its member state and requested the CHMP to prepare an Opinion, pursuant to Article 107 of Directive 2001/83/EC, as amended. Assessment report was circulated by France on 10 December 2009.

The procedure described in Article 107 of Directive 2001/83/EC, as amended, was applicable.

# 2. SCIENTIFIC DISCUSSION

## 2.1. Introduction

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the family of propionics derived from arylcarboxylic acid with analgesic and antipyretic 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 Member 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 French competent authority suspended these medicines from the French market on 12 January 2010.

Following a judgement of the French Council of State, stating that there was no emergency to suspend ketoprofen gel formulations before the end of the European procedure, the medicines were put back on the market on 26 January 2010 in France.

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.

## **2.2. Clinical 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.

### **2.2.1. Definition of Photoallergy**

For a better understanding of the issue of this procedure, a definition of photoallergy is presented below.

Cutaneous photosensitivity involves all the pathological phenomena connected to the interaction of a photosensitising substance present in the skin with radiation with an effective wavelength (U.V.A., U.V.B or visible). Photosensitivity is clinically responsible for photodermatosis, a cutaneous illness involving an exaggerated or abnormal sensitivity to light. The photoactive substance of exogenous origin reaches the skin through the bloodstream (medicines administered orally or by parenteral route) or following topical application (topical medicines, cosmetics, plant medicines).

The resulting cutaneous incidents can be broadly separated into two physiopathological mechanisms:

- phototoxicity, a photochemical reaction, the most frequent, caused by the direct effect of the absorption of light energy;
- photoallergy, an immunoallergic reaction to an antigen formed in the skin following luminous irradiation. It involves the T lymphocytes and is attributed to a type IV hypersensitive reaction to an allergen formed by the combination of photoactivated molecules and tissular proteins. Contrary to phototoxicity, the lesions can worsen following successive exposures to the substance in question, even in case of low light (Table I).

Both events really differ in term of time to onset, location and physiopathological mechanism:

Table I : Phototoxic or photoallergic reactions

<b>CRITERIA</b>	<b>PHOTOTOXICITY</b>	<b>PHOTOALLERGY</b>
Frequency	High All individuals can be affected	Low Rare, low percentage of the population
Mechanism	Physico-chemical reaction	Immunological reaction
Prior sensitisation	No	Yes
Factors required to trigger off the reaction: dose of light cutaneous concentration of a photosensitising product	High High	Low Low
Time to onset after exposure to the photosensitiser and light	Minutes to hours	24 hrs or more, progressively
Clinical appearance	Monomorphous, erythema with "sunburn" pain	Polymorphous, acute eczema with pruritus
Location	Photoexposed areas only	Photoexposed areas and possible extension to covered areas
Development	Rapid recovery in 8 to 10 days with: Regression on ending exposure to the sun with or without withdrawal of the medicine Regression on withdrawing the medicine with or without ending exposure to the sun.	Slow recovery over several weeks after withdrawing the medicine with possible persistence
Pigment disorders	Frequent	Unusual
Histologic lesions	Actinic erythema with unicellular necrosis of the epidermic cells (sunburn cells")	Lesions similar to those in contact dermatitis with spongiosis and exocytosis.
Future	Does not contraindicate continued treatment or reintroduction in case of effective protection from the sun.	Cross-photosensitisation between immunologically similar substances possible and risks of aggravation if medicine not definitively withdrawn.
Additional examinations Patch test Photo-patch test	No results Particularly highlights the photoallergy Photobiological testing adds little to imputability	The results are reliable in the case of photoallergies caused by topical medicines but much more random in case of oral administration.

## 2.2.2. Safety Data

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 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 1<sup>st</sup> January 2001 to 31<sup>st</sup> 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.

In responses to the above concerns, through a first list of questions, the MAHs provided the CHMP with data concerning their topical ketoprofen containing medicinal products (including name, formulation, dosage, full composition current approved SPC and PL, status). Sales figures per Member States, by year since 1993 were also provided.

In order to assess the risk of photoallergy reactions, the CHMP asked the MAHs to provide all cutaneous cases reported since launch, regardless of their seriousness and under the CIOMS form. Information concerning time to event, outcome, seriousness, concomitant medication and/or use of other cosmetic products including sunscreens, relevant medical history, possible contributing risk factors, available information on patch tests and photopatch tests were also requested. The MAHs provided the below information accordingly.

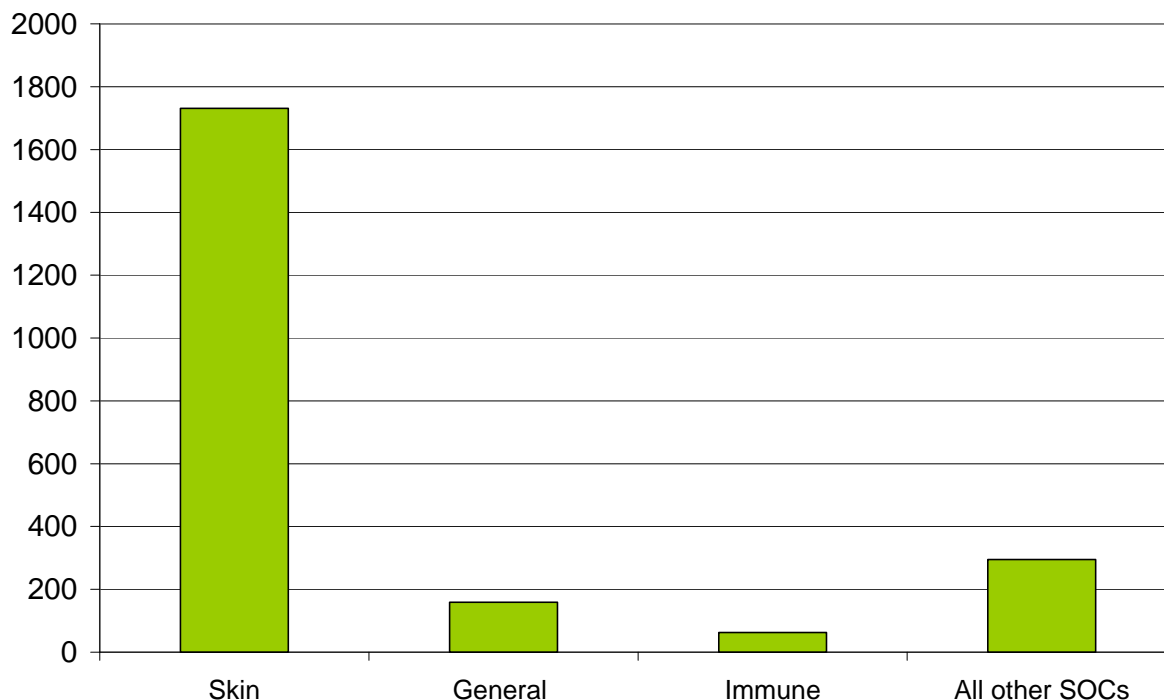
- the reported cases (and number of adverse events) by System Organ Class (SOC):

MAHs provided information about 2 248 Individual Case Safety Reports (ICSRs) from which 1 731 (77%) were from the MedDRA SOC "Skin and sub-cutaneous tissue disorders". ICSRs reported the events "skin reactions" but application site reaction or application site photosensitivity reaction can be also coded under the MedDRA SOC "General disorders and administration site conditions". Hypersensitivity reactions (allergic oedema, application site hypersensitivity) can be also coded under the MedDRA SOC "Immune system disorders". That is probably the reason, why the following most frequent SOC's were: General disorders and administration site conditions and Immune system disorders (table 2 and figure 1).

Table 2: Number and percentage of reports according MedDRA SOC

MedDRA - SOC Name	Number of reports	Percentage %
Skin and sub-cutaneous tissue disorders	1731	77
General disorders and administration site conditions	159	6,8
Immune system disorders	63	3
All other SOCs	295	13
<b>Total Number</b>	<b>2248</b>	<b>100</b>

Figure 1. Number of reports according to MedDRA SOC



According to summary information provided by MAHs “Photosensitivity reaction” was reported in 506 cases from 1731 skin reports (29%). Generalised eruption and disseminations of skin lesion to other than treated site were also reported. The most serious cases required hospitalisation.

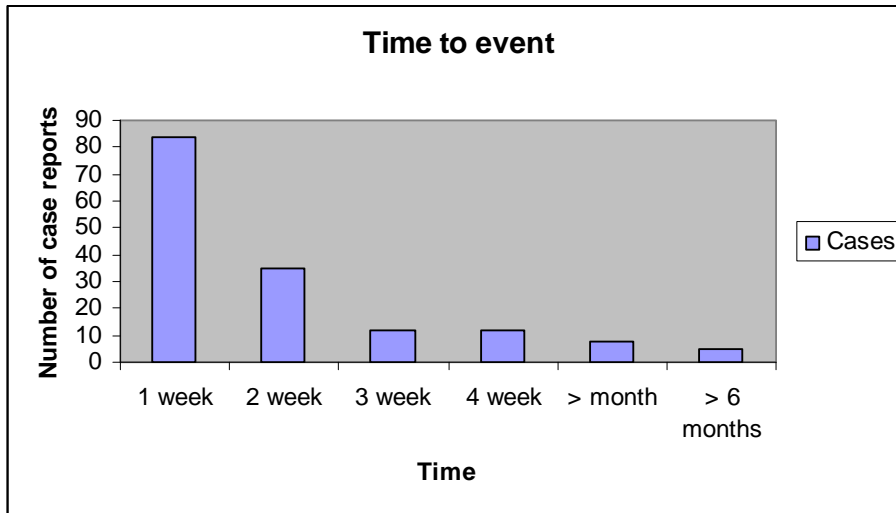
The CHMP noted that many reactions reported as dermatitis, rash, eczema, erythema and blisters without direct specification of the photocomponent can also represent photosensitive reactions and therefore the number of reactions selected by the MAHs as photosensitivity reactions could account for only incomplete part of all real photosensitivity reactions.

- the duration of treatment and time to event

Information on duration of treatment and time to event was available only in some ICSRs. Furthermore, some MAHs did not provide any information regarding duration of treatment and time to event. Data on time to event was provided only on 460 ICSRs from 1731 of MedDRA SOC Skin and sub-cutaneous tissue disorders. Mean time to onset was between 7 and 9,8 days. The 53-70% of cases occurred during first week of treatment, 95% of reports occurred until 4 weeks. There was a low number of isolated reports in which the event occurred months after the onset of the use of topical

ketoprofen. Detailed analysis by day distribution of cases according to time to event was done by one MAH on 155 ICSRs (Figure 2).

Figure 2 Time to event



Information regarding duration of treatment was provided only in 316 ICSRs. Duration of treatment was 7-9,9 days.

- Outcome and sequale

The recovery of the patient was reported in 56 % of cases (n=958), and recovery with sequelae is in 2,2% (n=37) of all reports. The events were reported as ongoing or not resolved in 11,5 % of cases (n=60). The outcome of the event is unknown in 30% of the cases (n=509).

Table 3 Outcome – number of ICSRs

	Number of ICSRs	Percentage
Resolved	958	56
Not resolved/ongoing	195	11,5
Resolved with sequelae	37	2,5
Unknown	509	30

- Seriousness

The MAHs provided information on seriousness for 1438 ICSRs.

Table 4 Seriousness – number of reports

	Serious	Non serious	Total
Number of reports	487	951	1 438

To compare the incidence reporting between Member States, an analysis on frequency by Member States was requested, with any possible explanation of the difference between Member States.

The mechanism the photoallergic reaction induced topical ketoprofen formulation was also assessed, as well as all other available data (i.e pre-clinical and any other clinical data, including clinical trials and pharmacoepidemiological studies) relevant to evaluate the risk of serious cutaneous reactions, in particular photoallergy reactions.



Besides, the MAHs provided the CHMP with a critical assessment on the impact of serious cutaneous reactions (namely prolonged hospitalisation for instance), including photoallergy reactions, on the benefit/risk of ketoprofen topical formulations with the possibility to include benefit data in the scope of that question.

Finally, information and details of any specific measures already taken in order to minimise the risk of photoallergy reactions in patient using topical ketoprofen were requested by the CHMP as well as an analysis of the impact of such measures.

In the same way, the CHMP requested the MAHs to provide proposals and justification with supportive evidence for any risk minimisation measures, including changes to the Summary of Product Characteristics, Labelling and Package Leaflet, which could be implemented in order to improve the benefit/risk of ketoprofen containing medicinal products for topical use. The way to monitor and assess the impact of such measures was also part of subsequent list of questions.

Since some questions were still not satisfactorily explored, a final list of question was addressed to the MAHs by the CHMP to which the MAHs responded providing information regarding the established efficacy of topical ketoprofen relative to other topical NSAIDs. The three remaining questions pertained to safety and concerned the pattern of use (in terms of demographics and indications, including any possible explanation of the difference in reporting rates of cutaneous Adverse Drugs Reactions (ADRs) in the different EU countries), and the reason of the failure of risk minimisation measures implemented in France and experiences of RMM in other countries and finally, in case of maintenance of the MAs, how the effectiveness of the RMMs will be followed given the limitations of spontaneous ADR reporting rates for this purpose.

In addition the CHMP also assessed the risk of co-sensitisation with octocrylene. 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 the assessed data, including published data, the CHMP concluded that there is also a risk of associated-reaction appearing with octocrylene.

### **2.2.3. Discussion**

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 A 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 and life-time contraindication of tiaprofenic acid and fenofibrate for the patient.

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 willing 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; Bennisar 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 perfumes
  - 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, 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 communications 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 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 1<sup>st</sup> 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.

### **2.3. Clinical 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.

### **2.4. Benefit Risk Assessment**

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 relieve 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 outweighs 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.

## **2.5. Communication plan**

As part of this review procedure, a wording of a Direct Healthcare Professional Communication was designed to inform prescribers of the amendments of the Marketing Authorisations, the photosensitivity risk associated with the product and the risk of co-sensitisation with octocrylen, to be sent on 4 August 2010 to relevant health care professionals.

Each Member State will ensure that the relevant information is included in the translation in their National Language, as applicable.

## **2.6. Changes to Product Information**

As part of the procedure, the CHMP recommended that all the below sections of the SPC, labelling and package leaflet should be amended and harmonised in the EU. The key amendments are described below:

### **Changes into the SPC:**

#### **Section 4.3      Contraindications**

...[ ]...

Section 4.3 of the SPC should contain the following:

- history of any photosensitivity reaction
- known hypersensitivity reactions, such as symptoms of asthma, allergic rhinitis to ketoprofen, fenofibrate, tiaprofenic acid, acetylsalicylic acid, or to other NSAID
- history of skin allergy to ketoprofen, tiaprofenic acid, fenofibrate or UV blocker or perfumes
- sun exposure, even in case of hazy sun, including UV light from solarium, during the treatment and 2 weeks after its discontinuation

#### 4.4 Special warnings and special precautions for use

...[ ]...

Section 4.4 of the SPC should contain the following:

- Hands should be washed thoroughly after each application of the product.
- Treatment should be discontinued immediately upon development of any skin reaction including cutaneous reactions after co-application of octocrylene containing products
- 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.

#### 4.8 Undesirable effects

...[ ]...

Section 4.8 of the SPC should contain the following:

- Local skin reactions such as erythema, pruritis and burning sensations.
- Cases of more severe reactions such as bullous or phlyctenular eczema which may spread or become generalized have occurred rarely.
- Hypersensitivity reactions.
- Dermatological: photosensitisation

#### **Changes into the Labelling:**

A pictogram on the outer box and on the immediate packaging should be introduced, as well as the introduction of a warning on the outer box and on the immediate packaging reading as follows:

*Do not expose treated areas to sunlight (even hazy) including UV from solarium during the treatment and the 2 weeks after its discontinuation*

#### **Changes into the PL:**

The **PL** should be amended according to the above SPC changes, reading as follows:

#### **Section 2 - BEFORE YOU <TAKE> <USE> X**

##### **Do not <take> <use> X**

...[ ]...

- Do not use if history of allergy to ketoprofen, tiaprofenic acid, fenofibrate, UV blockers or perfumes is known
- Stop using X immediately if you experience any skin reaction including cutaneous reactions after co-application of octocrylene containing products (Octocrylene is one of the excipient of several cosmetic and hygiene 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.)
- Do not expose treated areas to sunlight or UV light from solarium during the treatment and the 2 weeks following its discontinuation.

##### **Take special care with X**

...[ ]...

- The exposure to the sun (even hazy) or to UVA of areas in touch with X can induce potentially serious cutaneous reactions (photosensitisation). Therefore it is necessary to:  
-protect treated areas by wearing clothing during the treatment and for two weeks after its discontinuation to avoid any risk of photosensitisation.  
-wash your hands thoroughly after each application of X.
- Treatment should be discontinued immediately upon development of any skin reaction after application of X.

#### **Section 4 - POSSIBLE SIDE EFFECTS**

...[ ]...

- allergy skin reactions
- severe skin reaction during an exposure to the sun light
- Cases of more severe reactions such as bullous or phlyctenular eczema which may spread or become generalized have occurred rarely

## **2.7. Conditions to the Marketing Authorisations**

National Competent Authorities, coordinated by the Reference Member State where applicable, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

### **PSURs**

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.

### **Educational tools**

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.

### **Legal status**

All ketoprofen medicinal products for topical use should be subject to medical prescription.

### **DHPC**

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

In view of the divergent outcomes on the effectiveness of the measures previously applied by some Member States, the CHMP considers that it is important for the Committee to review and conclude on the effectiveness of the measures that are now being recommended at Community level. Therefore the **MAHs should provide the following to the CHMP:**

### **Cumulative analysis of photosensitivity reactions**

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.

### **Surveillance study of photocontact dermatitis leading to hospitalization in Europe with a special focus on topical ketoprofen and other topical NSAIDs, including evaluation of severe photosensitivity reactions**

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 1<sup>st</sup> 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.

### 3. OVERALL CONCLUSION

Having considered the overall submitted data provided by the MAHs in writing and during oral explanations as well as the data from the 2 French pharmacovigilance surveys, the French benefit risk reassessment, and the discussions within the Committee, the CHMP concluded the following:

- 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 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 the Opinion.

### 4. ANNEXES

The list of the names of the medicinal products, Marketing Authorisation Holders, pharmaceutical forms, strengths and route of administration in the Member States are set out in Annex I to the Opinion.