HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

20 March 2013

KETUM 2.5%, gel

B/1 tube of 60 g (CIP: 333 549-7)
B/1 tube/dispenser of 60 g (CIP: 344 444-7)
B/1 tube/dispenser of 120 g (CIP: 344 447-6)

Applicant: MENARINI FRANCE

INN	**ketoprofen**
ATC Code (2012)	**M02AA10 (anti-inflammatory preparations, non-steroids for topical use)**
Reason for the request	**Renewal of inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17)
Indication concerned	**"Symptomatic treatment of superficial tendinitis.** **Symptomatic treatment in benign trauma: sprains, contusions.** **Symptomatic treatment of small-joint osteoarthritis.** **Symptomatic treatment of acute low back pain.** **Treatment of postsclerotherapeutic phlebitis in cases of intense inflammatory reaction."**

Transparency Committee conclusions:

Actual Benefit	Insufficient for reimbursement by National Health Insurance in all the Marketing Authorisation indications (superficial tendinitis, benign trauma, small-joint osteoarthritis, low back pain and postsclerotherapeutic phlebitis).
Improvement in Actual Benefit	**Not applicable**
Therapeutic use	Not applicable
Recommendations	The Transparency Committee does not recommend continued inclusion of KETUM gel on the list of medicines reimbursed by National Health Insurance in all its indications. This opinion applies to KETUM generics.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date of initial Marketing Authorisation: 22/01/1991 (national)
Prescribing and dispensing conditions/ special status	List II

ATC Classification	2012	
	M	Musculo-skeletal system
	M02	Topical products for joint and muscular pain
	M02A	Topical products for joint and muscular pain
	M02AA	Anti-inflammatory preparations, non-steroids for topical use
	M02AA10	ketoprofen

02 BACKGROUND

Examination of the proprietary medicinal products included again on the list of medicines refundable by National Health Insurance for a 5-year period starting on 13/06/2007 (Official Gazette of 09/07/2008).

Regulatory history

In December 2009, AFSSAPS decided to suspend the Marketing Authorisation of ketoprofen gels, considering the risk of onset of serious cutaneous adverse effects, and photoallergic reactions in particular, to be greater than the expected benefit (their efficacy having been assessed as low to moderate based on available placebo-controlled clinical studies).[1]

A reassessment of the benefit/risk ratio of these proprietary medicinal products conducted between 2001 and 2009 showed that the risk of photoallergic reactions, which had been identified in 1993, remained despite the many adopted measures: changes to the Summary of Product Characteristics (SPC) and to the package leaflet (twice), the addition of a pictogram on the packaging, and the sending out of a letter to healthcare professionals in 2003. Moreover, in the course of this reassessment a new issue was identified, namely the existence of an allergy associated with octocrylene (a sunscreen and chemical anti-UVA filter). The decision to suspend Marketing Authorisation took effect on 12 January 2010, pending the results of the European assessment requested by AFSSAPS, given that these products were on sale in many countries.

The pharmaceutical company MENARINI, who hold the licence for KETUM, in late December 2009 filed an application with the Council of State for interim measures asking for the decision to be suspended to enable them to challenge the decision. On 26 January 2010, the Council of State suspended this decision, authorising sales of ketoprofen gels to be resumed.

In July 2010, at the end of the European reassessment procedure[2], the EMA concluded that while the photosensitivity reactions to topical medicines containing ketoprofen did constitute major adverse effects, the benefit/risk ratio of these preparations remained favourable.

[1] AFSSAPS: Suspension of Marketing Authorisation for ketoprofen gels – letter to healthcare professionals. 18 December 2009.
[2] EMA. Assessment report for ketoprofen containing medicinal products (topical formulations). 29/11/2010

On 29 November 2010, the European Commission ratified the EMA's conclusions regarding allowing ketoprofen-containing medicinal products for topical use to remain on the market.
This upholding of the decision was accompanied by European harmonisation of the SPCs for these proprietary medicinal products, in the following sections in particular:
- 4.3 Contraindications,
- 4.4 Special warnings and precautions for use,
- 4.8 Undesirable effects.

Thus the antecedents of photosensitivity reactions have been included in the contraindications, and the reference to stopping treatment in the event of a cutaneous reaction when co-administered with products containing octocrylene has been added to the warnings and precautions for use (cf. appendix of changes to the SPC for KETUM).

In December 2011, AFSSAPS sent out a further letter to prescribers, reminding them of its recommendations aimed at reducing the risk of photosensitivity reactions:
"Prescribers must strictly observe the following contraindications when prescribing ketoprofen-containing topical preparations:

- History of any photosensitivity reaction,
- Known hypersensitivity reactions, such as symptoms of asthma and allergic rhinitis in response to ketoprofen, fenofibrate, tiaprofenic acid, acetylsalicylic acid, or to other NSAIDs,
- History of skin allergy to ketoprofen, tiaprofenic acid, fenofibrate, or UV blocker or perfumes,
- Known allergy to any of the excipients,
- Damaged skin, regardless of the cause of the damage: oozing skin lesions, eczema, infected lesions, burns or wounds.

Prescribers and pharmacists should remind patients of the importance of taking preventive measures against the risk of photosensitivity reactions during treatment with topical ketoprofen[3]:

- Do not expose treated areas to the sun, even hazy sun, or to UVA rays in a solarium throughout the period of treatment and for two weeks after stopping it.
- Protect treated areas from the sun by wearing clothing.
- Wash hands thoroughly after each application of the gel.
- Do not apply ketoprofen gels under an occlusive dressing.
- Stop the treatment immediately in the event of onset of a skin reaction."

The next European reassessment of these medicinal products is planned for 2013.

03 THERAPEUTIC INDICATIONS

"Symptomatic treatment of superficial tendinitis.
Symptomatic treatment in benign trauma: sprains, contusions.
Symptomatic treatment of small-joint osteoarthritis.
Symptomatic treatment of acute low back pain.
Treatment of postsclerotherapeutic phlebitis in cases of intense inflammatory reaction."

[3] These recommendations appear in the French SPCs of all ketoprofen gels since 2001, apart from the reference to cutaneous reactions appearing after co-administration of products containing octocrylene which was added to SPCs following ratification by the European Commission of the opinion delivered by EMA's Committee for Medicinal Products for Human Use (CHMP).

04 DOSAGE

“Only for use by adults (over the age of 15 years).
For topical use.
Rub the gel in by gentle and prolonged massage in the painful or inflamed area.
Wash hands thoroughly after use.

Tube:
Sprains, contusions, postsclerotherapeutic phlebitis in cases of intense inflammatory reaction: two daily applications of 2 g of gel (i.e. about 5 cm of gel).
Superficial tendinitis: two daily applications of 4 g of gel (i.e. about 10 cm of gel).
Small-joint osteoarthritis: three daily applications of 4 g of gel (i.e. about 10 cm of gel).
Acute low back pain: Three applications of 5 g (i.e. about 12 cm of gel) in the first 3 days, then two applications of 5 g of gel in the following 4 days.

Tube/dispenser:
1 dose = 1.2 g of gel, i.e. 30 mg of ketoprofen.
The dosage is 3 to 12 doses in 2 to 3 daily applications, depending on the indications:
Sprains, contusions, postsclerotherapeutic phlebitis in cases of intense inflammatory reaction: 3 daily doses.
Superficial tendinitis: 6 daily doses.
Small-joint osteoarthritis: 9 daily doses.
Acute low back pain: 12 doses a day for the first few days, then 8 daily doses.”

05 THERAPEUTIC NEED

Tendinitis

Management of tendinitis is local and combines, in the first place, physiotherapy sessions and the prescribing of anti-inflammatories to relieve pain and reduce inflammation. Rest and wearing a brace to protect the joint generally suffice. Intramuscular glucocorticoid injections in the area of the trauma are sometimes given.

Surgical intervention is indicated in cases of ruptured tendons (ruptured Achilles, patellar or shoulder tendon). The use of NSAIDs is justified particularly at the acute stage.

Sprains and contusions

In the treatment of benign sprains, NSAID-based topical preparations can be effective in reducing swelling and pain. They constitute an alternative to the usual drug treatments and are compatible with wearing a removable splint. Paracetamol is the first-line systemic analgesic. The superiority of NSAIDs over analgesics has not yet been proven. They should therefore be used in moderation, taking into account the risk of adverse effects according to the patient's pathophysiological needs and any therapies that are currently being applied.

Small-joint osteoarthritis

Small-joint osteoarthritis can be managed with physiotherapy. Analgesics are used as first-line drugs. Short courses of non-steroidal anti-inflammatories are reserved for the most painful flare-ups of the illness.

Postsclerotherapeutic phlebitis

The principle of sclerotherapy is to suppress the reflux function in the superficial venous system in the lower limbs. The purpose of sclerotherapy is to shrink the fibres in the treated vein, eventually closing off the venous lumen. Injection into a varicose vein of a chemical, usually a surfactant, ultimately produces an inflammatory reaction in the endothelial wall of the vein.

Recourse to topical NSAIDs may be justified.

Low back pain

In acute forms, paracetamol is the first-line treatment. If paracetamol should prove insufficient, an NSAID may be prescribed as a second-line treatment, either alone or combined with an analgesic.

In chronic forms, non-pharmacological treatments have a major role to play. Recourse to NSAIDs should be confined to painful flare-ups that fail to respond to paracetamol or to other analgesic measures. NSAIDs should be prescribed for the minimum necessary duration and at the lowest effective dose.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The NSAIDs in question are for topical administration:

Proprietary medicinal products INN	Indications	AB
ADVIL 5% gel Tubes of 60 g and 100 g ANTARENE 5% gel Tubes of 50 g and 100 g DOLGIT 5%, cream Tube of 50 g Ibuprofen	- Symptomatic treatment in benign trauma: sprains, contusions. - Symptomatic treatment of tendinitis. - Symptomatic treatment of small-joint osteoarthritis (DOLGIT only)	Moderate: Tendinitis of the upper and lower limbs Low: Benign trauma: sprains, contusions Painful osteoarthritis in the fingers and knees (DOLGIT only)
FLECTOR 1% gel Tube of 60 g 100 g pressurised can XENID 1% gel Tube of 60 g VOLTAREN EMULGEL 1% gel Tube of 50 g 100 ml pressurised can Diclofenac	- Tendinitis of the upper and lower limbs. - Postoperative and post-traumatic oedema. - Symptomatic treatment of painful osteoarthritis in the fingers and knees (VOLTAREN EMULGEL only)	Moderate: - Tendinitis of the upper and lower limbs. - Postoperative and post-traumatic oedema. Low: - Painful osteoarthritis in the fingers and knees
GELDENE 0.5%, gel Tube of 50 g Piroxicam	- Symptomatic treatment of superficial tendinitis. - Symptomatic treatment in benign trauma: sprains, contusions.	Moderate: - Tendinitis of the upper and lower limbs Low: - Benign trauma: sprains, contusions
NIFLUGEL 2.5% gel Tube of 60 g Niflumic acid	- Symptomatic treatment of superficial tendinitis. - Symptomatic treatment in benign trauma: sprains, contusions	Moderate: - Superficial tendinitis. Low: - Benign trauma: sprains, contusions
PROFENID 2.5%, gel Tube of 60 g Ketoprofen (taken off the market on 31/03/2011)	- Symptomatic treatment in benign trauma: sprains, contusions.	**Low:** Benign trauma: sprains, contusions **(reassessment applied for on the initiative of the Transparency Committee)**

As a reminder, the actual benefit of fixed topical combinations of DEXTRARINE, PHENYLBUTAZONE, CORTISAL and PERCUTALGINE is insufficient in all their indications.

06.2 Other health technologies

Not applicable.

Conclusion

KETUM 2.5% gel and its generics are the only topical NSAIDs having all the following indications: symptomatic treatment of superficial tendinitis, sprains and contusions, small-joint osteoarthritis, acute low back pain and postsclerotherapeutic phlebitis in cases of rare inflammatory reactions.

The Committee considers that the other topical NSAIDs whose indications and actual benefit are given in the above table constitute clinically relevant comparators of KETUM gel.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

KETUM 2.5% gel is currently marketed by MENARINI (with formulations containing excipients and names that differ according to country) in every European country except the Netherlands (where it has never been sold).

08 SUMMARY OF PREVIOUS ASSESSMENTS

Opinion on renewal of inclusion: 04 July 2007

"In accordance with previous opinions issued for medicinal products in the same category, the actual benefit of KETUM 2.5% gel is:

- moderate in the symptomatic treatment of superficial tendinitis
- low in small-joint osteoarthritis, sprains, contusions and postsclerotherapeutic phlebitis.

As regards the indication symptomatic treatment of acute low back pain, in light of the available data,[4] the Transparency Committee considers the actual benefit of this medicinal product in this indication to be low.

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications and at the dosages in the Marketing Authorisation."

Opinion on renewal of inclusion: 17 October 2001

"The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications and at the dosages in the Marketing Authorisation."

[4] Ph. Brissaud, A. Grassiet. Lombalgies aigües discales. Synoviales 1995

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

The Applicant provided:

- the results of three meta-analyses (Moore et al., 1998; Mason et al., 2004; and August 2004) and one clinical study (Patel et al., 1996), which were taken into account in the EMA's benefit/risk reassessment in 2010;
- one meta-analysis (Massey et al., 2010);
- one literature review (Altman et al., 2011) of no great relevance for assessing the size of the effect of topical NSAIDs in osteoarthritis, which will not be described.

Moore et al., 1998[5]

This meta-analysis included 86 randomised, controlled clinical studies versus placebo or active treatment (another topical NSAID or oral NSAID), which evaluated the efficacy and tolerability of topical NSAIDs in pain associated with acute trauma (sprains, contusions, sports injuries and soft-tissue damage) and chronic conditions (chronic rheumatism, osteoarthritis). Efficacy in chronic rheumatic disorders, including osteoarthritis, was evaluated after two weeks of treatment. The superiority of topical NSAIDs over placebo in terms of the number of responder patients, defined as the number of patients with at least 50% pain reduction, was revealed in this meta-analysis.

Table 1. Efficacy of topical NSAIDs vs. placebo in acute trauma pain and in chronic pain – results from the Moore meta-analysis

	Studies (n)	Patients (n)	Response with placebo (%)	Response with treatment (%)	Absolute benefit (%)	Relative benefit (95% CI)
Acute trauma pain	37	3239	39	71	32	1.7 (1.5 to 1.9)
Chronic rheumatic pain	12	1097	30	65	35	2 (1.5 to 2.7)

The percentage of responders with ketoprofen gel was 74% versus 36% with placebo, i.e. an absolute difference of 38% (relative benefit of 2 [1.5; 2.6]) in acute pain. No results were provided for ketoprofen in chronic pain.

Mason et al., May 2004[6] and August 2004[7]

The meta-analysis from May 2004 included 26 studies which evaluated the efficacy and tolerability of topical NSAIDs in acute trauma, and the one from August 2004 looked at 15 studies conducted in chronic rheumatic disorders, including osteoarthritis.

Efficacy was evaluated as in Moore's meta-analysis. Specific results for ketoprofen were only provided in the meta-analysis from May 2004; the percentage of responders with ketoprofen gel was 77.77% versus 39.45% with placebo, i.e. an absolute difference of 38.32% (relative benefit of 2.1 [1.7; 2.5]).

[5] Moore et al. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ 1998;316:333-8.
[6] Mason et al. Topical NSAIDs for acute pain: a meta-analysis. BMC Fam Pract 2004;5:10.
[7] Mason et al. Topical NSAIDs for chronic musculoskeletal pain: review and meta-analysis. BMC Musculoskel Dis 2004;5:28.

Table 2. Efficacy of topical NSAIDs vs. placebo in acute trauma pain and in chronic pain – results from the meta-analyses by Mason

	Studies (n)	Patients (n)	Response with placebo (%)	Response with treatment (%)	Absolute benefit (%)	Relative benefit (95% CI)
Acute trauma pain (May 2004)	26	2853	39	65	26	1.6 (1.4 to 1.7)
Chronic rheumatic pain (August 2004)	14	1051	26	48	22	1.9 (1.7 to 2)

The results from these three meta-analyses showed the superiority of topical NSAIDs, including ketoprofen, over placebo.

Study by Patel et al., 1996[8]
This randomised, open-label clinical study evaluated the efficacy of ketoprofen gel (2.5%), piroxicam gel (0.5%) and diclofenac gel (1%) administered three times daily for 5 days in patients with acute trauma. The investigator judged the pain to have been significantly improved in:
74% of cases with ketoprofen gel
71% of cases with diclofenac gel
65% of cases with piroxicam gel.
Given its methodology and its endpoints, it is not possible to draw any conclusions from this study as regards the relative efficacy of topical NSAIDs.

Among the new data provided by the applicant since the EMA reassessment:

- Cochrane meta-analysis (Massey et al., 2010)[9]

This meta-analysis included 47 double-blind, randomised studies that evaluated the efficacy of topical NSAIDs versus placebo or active treatment in acute pain, in particular pain resulting from sprains. The proportion of responder patients (50% pain relief) was 65% [31-100] with topical NSAIDs versus 43% [8-83] with placebo, i.e. an absolute benefit of 22% and a relative benefit of 1.5 [1.4 to 1.6]. The proportion of responder patients with ketoprofen was 73% [57-89] versus 47% [17-73] with placebo, i.e. an absolute benefit of 26% and a relative benefit of 1.6 [1.4 to 1.8].

09.2 Safety/Adverse effects

National pharmacovigilance surveys conducted from 1993 (the year in which KETUM gel was first marketed) revealed serious cases of photoallergy occurring with topical forms of ketoprofen.
The survey covering the period from 01/03/1993 to 31/08/1995 revealed a rate of cutaneous adverse effect (AE) notifications of 0.023/1000, i.e. 1 cutaneous effect in 42,800 treated patients (data gathered by Regional Pharmacovigilance Centres – CRPVs).
Over the period from 31/08/1995 to 31/08/1996, the rate of notifications was 0.020/1000, i.e. 1 cutaneous effect in 49,235 treated patients (data gathered by CRPVs), and over the period from 01/09/1996 to 31/08/2000 the rate of notifications was 0.028/1000, i.e. 1 cutaneous effect in 35,005 treated patients (cases gathered by the CRPV and Menarini France).
During the period 2001-2009 (French period of assessment of the benefit/risk ratio), 467 AEs (55%) were reported with ketoprofen gel, including 386 cutaneous AEs (83%). Of these cutaneous AEs, 257 were serious. In 5% of cases, the use of an occlusive dressing was reported, in spite of the precaution for use “Do not apply ketoprofen gels under an occlusive dressing”. The majority of patients got better without sequelae.
Photoallergy accounted for 44% (169) of the cutaneous AEs and 66% (112) of the serious cutaneous AEs. This AE, though rare, could prove serious and lead to hospitalisation or work stoppage. Exposure to sun was reported as a contributory factor in the majority of cases. In

[8] Patel et al. Comparison of ketoprofen, piroxicam, and diclofenac gels in the treatment of acute soft-tissue injury in general practice. Clin Ther 1996;18(3):497-507.
[9] Massey et al. Topical NSAIDs for acute pain in adults. Cochrane Database Sys Rev 2010;6:CD007402.

153 cases (90%), a cure was obtained without sequelae after treatment with systemic and/or local corticosteroids.

According to data provided by the Marketing Authorisation holders for ketoprofen gel as part of the EMA's reassessment of the benefit/risk ratio, 2248 AEs, including 1731 cutaneous effects, were reported since the various proprietary medicinal products came onto the market. Photosensitivity reactions accounted for 29% of the AEs, i.e. 506 cases. In 53 to 70% of the cases, the cutaneous AEs were reported during the first week of treatment.

Analysis of the latest pharmacovigilance safety update report (PSUR) covering the period from 1 August 2010 to 30 September 2011 yielded an estimate for the number of patients treated with KETUM gel in France of 1,501,481. uring this period, a total of 62 observations accounting for 112 AEs were notified, including 48 observations considered to be serious, corresponding to 89 serious AEs.Cutaneous AEs were notified in 38 patients (61 AEs), i.e. 1 serious cutaneous case in 39,513 treated patients. The incidence of photoallergy was 1.8×10^{-5} (27 cases in 1,501,481 treated patients). Between 1 October 2011 and 30 September 2012, 7 photoallergy cases were observed in 1,045,126 treated patients (incidence of 0.7×10^{-5}).

To date, according to ANSM data, no similar pharmacovigilance issues have ever been flagged in France with other topical NSAIDs.

09.3 Summary & discussion

The data provided as part of the application for renewal of the inclusion of KETUM 2.5% gel (ketoprofen) on the list of proprietary medicinal products refundable by National Health Insurance showed that its efficacy in the treatment of the pain associated with acute trauma or chronic disorders was moderate or even poor versus placebo. In this context, the therapeutic objective is to treat the pain as effectively as possible and over short periods.

The pharmacovigilance data revealed notifications of persistent cutaneous AEs despite risk minimisation measures (strengthening of the contraindications and warnings, addition of a pictogram, letters to prescribers) adopted by ANSM on repeated occasions. The identified risk of photosensitisation (though its frequency is rare) seems to be preponderant with ketoprofen gel (ANSM Assessment Report, case study[10]). No pharmacovigilance flag has ever been reported with any of the other available topical NSAIDs (including diclofenac in topical form, which is the most heavily prescribed active ingredient,[11] ibuprofen, etc.), which therefore constitute alternatives with a better cutaneous tolerability profile.

[10] Ruth L DIAZ et al. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. Contact Dermatitis 2006; 54: 239-243.

[11] A total of over 15 million units sold through pharmacies in 2011, including over 9 million units of VOLTAREN EMULGEL, as opposed to around 1,700,000 units of KETUM gel.

09.4 Usage/prescription data

According to IMS-EPPM data (moving annual total to August 2012), KETUM gel (taking all presentations together) accounted for 786,000 prescriptions. This refers to the most heavily prescribed ketoprofen gel (KETUM accounts for 83% of prescriptions). The mean dosage was 3.7 daily applications, and the mean number of days for which prescriptions were issued was 21.4.

Sales of KETUM gel are falling:

	2009	2010	2011	2012 (January to September)
Number of tubes sold in pharmacies	3,092,559	2,259,515	1,741,408	1,100,551

Source: GERS

010 THERAPEUTIC USE

In view of:

- the need for more effective treatments over shorter periods for the management of pain in the disorders concerned,
- the poor to moderate efficacy demonstrated principally versus placebo,
- the continuing risk of serious cutaneous adverse effects (photoallergy),
- and the existence of alternatives (other topical NSAIDs) for which no such pharmacovigilance flags have ever been reported,

the Transparency Committee considers that KETUM gel has no place in the management of superficial tendinitis, sprains and contusions, small-joint osteoarthritis, postsclerotherapeutic phlebitis or low back pain.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee considers that the conclusions in its previous opinion have been modified as follows:

011.1 Actual benefit

Superficial tendinitis

Tendinopathy causes pain and a greater or lesser degree of functional impairment.

According to its Marketing Authorisation indication, KETUM gel is intended as a local symptomatic treatment.

In view of:

- the need for more effective treatments over shorter periods for the management of pain in this disorder,
- an efficacy similar to that of other topical NSAIDs, which is moderate or even poor versus placebo,
- a continuing cutaneous risk, particularly of serious photoallergy, despite the measures taken by the ANSM,

the Transparency Committee considers that KETUM gel's efficacy/adverse effects ratio is inferior to that of other available topical NSAIDs, in respect of which there is no evidence of any photoallergy being flagged up.

There are treatment alternatives, including other topical NSAIDs against whose pharmacovigilance record there are no flags in terms of serious cutaneous reactions, in particular photoallergic reactions (diclofenac, ibuprofen, etc.). KETUM gel therefore has no place in the management of tendinitis.

This proprietary medicinal product has no public health benefit.

Taking account of these points, the Committee considers that the actual benefit of KETUM 2.5% gel in the symptomatic treatment of superficial tendinitis is, compared with the treatment alternatives, insufficient to justify reimbursement by National Health Insurance.

Benign trauma: sprains and contusions

Most sprains are benign trauma lesions with a rapid favourable course, but which can be very painful.

According to its Marketing Authorisation indication, KETUM gel is intended as a local symptomatic treatment.

In view of:
- the need for more effective treatments over shorter periods for the management of pain in this disorder,
- an efficacy similar to that of other topical NSAIDs, which is moderate or even poor versus placebo.
- a continuing cutaneous risk, particularly of serious photoallergy, despite the measures taken by the ANSM,

the Transparency Committee considers that KETUM gel's efficacy/adverse effects ratio is inferior to that of other available topical NSAIDs in respect of which there is no evidence of any photoallergy being flagged up.

There are treatment alternatives, including other topical NSAIDs against whose pharmacovigilance records there are no flags in terms of serious cutaneous reactions, in particular photoallergic reactions (diclofenac, ibuprofen, etc.). KETUM gel therefore has no place in the management of sprains or contusions.

This proprietary medicinal product has no public health benefit.

Taking account of these points, the Committee considers that the actual benefit of KETUM 2.5% gel in symptomatic treatment in benign trauma (sprains and contusions) is, compared with treatment alternatives, insufficient to justify reimbursement by National Health Insurance.

Small-joint osteoarthritis

Small-joint osteoarthritis can be disabling and entail a deterioration in the quality of life.

According to its Marketing Authorisation indication, KETUM gel is intended as a local symptomatic treatment.

In view of:
- the need for more effective treatments over shorter periods for the management of pain in this disorder,
- an efficacy similar to that of other topical NSAIDs, which is moderate or even poor versus placebo,
- a continuing cutaneous risk, particularly of serious photoallergy, despite the measures taken by the ANSM,

the Transparency Committee considers KETUM gel's efficacy/adverse effects ratio to be inferior to that of other available topical NSAIDs in respect of which there is no evidence of any photoallergy being flagged up.

There are treatment alternatives, including other topical NSAIDs against whose pharmacovigilance records there are no flags in terms of serious cutaneous reaction, in particular photoallergic reactions (diclofenac, ibuprofen, etc.). KETUM gel therefore has no place in the management of small-joint osteoarthritis.

This proprietary medicinal product has no public health benefit.

Taking account of these points, the Committee considers that the actual benefit of KETUM 2.5% gel in the symptomatic treatment of small-joint osteoarthritis is, compared with the treatment alternatives, insufficient to justify reimbursement by National Health Insurance.

Postsclerotherapeutic phlebitis

Postsclerotherapeutic phlebitis can cause pain and a greater or lesser degree of functional impairment.

According to its Marketing Authorisation indication, KETUM gel is intended as a local symptomatic treatment.

In view of:
- the need for more effective treatments over shorter periods for the management of pain in this disorder,
- an efficacy similar to that of other topical NSAIDs, which is moderate or even poor versus placebo,
- a continuing cutaneous risk, particularly of serious photoallergy, despite the measures taken by the ANSM,

the Transparency Committee considers that KETUM gel's efficacy/adverse effects ratio is inferior to that of other available topical NSAIDs in respect of which there is no evidence of any photoallergy being flagged up.

There are treatment alternatives, including other topical NSAIDs against whose pharmacovigilance records there are no flags in terms of serious cutaneous reactions, in particular photoallergic reactions (diclofenac, ibuprofen, etc.). KETUM gel therefore has no place in the management of post sclerotherapeutic phlebitis.

This proprietary medicinal product has no public health benefit.

Taking account of these points, the Committee considers that the actual benefit of KETUM 2.5% gel in the symptomatic treatment of postsclerotherapeutic phlebitis is, compared with the treatment alternatives, insufficient to justify reimbursement by National Health Insurance.

Acute low back pain[12]

Acute low back pain is a benign condition that resolves itself spontaneously in most patients. Occasionally it develops into a potentially disabling chronic form.

According to its Marketing Authorisation indication, KETUM gel is intended as a local symptomatic treatment.

In view of:
- the need for more effective treatments over shorter periods for the management of pain in this disorder,
- its at best moderate to poor efficacy versus placebo,
- a continuing cutaneous risk, particularly of serious photoallergy, despite the measures taken by the ANSM,

the Transparency Committee considers KETUM gel's efficacy/adverse effects ratio to be inferior to that of available alternative therapies (cf. section 5).

There are medicinal and non-medicinal treatment alternatives (cf. section 5). KETUM gel therefore has no place in the management of acute low back pain.

This proprietary medicinal product has no public health benefit.

Taking account of these points, the Committee considers that the actual benefit of KETUM 2.5% gel in the symptomatic treatment of acute low back pain is, compared to the treatment alternatives, insufficient to justify reimbursement by National Health Insurance.

011.2 Improvement in actual benefit

Not applicable.

011.3 Target population

Not applicable.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee does not recommend continued inclusion of KETUM gel on the list of medicines refundable by National Health Insurance in all its Marketing Authorisation indications.

This opinion applies to the generics of KETUM gel included in the list of proprietary medicinal products qualifying for reimbursement.

The Committee decides to reassess PROFENID gel, another ketoprofen-based topical medicinal product.

[12] KETUM gel is the only topical NSAID to have this indication.