



ketoprofen gels

REGULATORY PROBLEMS

Unfortunately back on the French market

● **Ketoprofen gels are more harmful than beneficial, and their withdrawal from the French market in late 2009 was a welcome measure. Unfortunately, they were back on the market in early 2010 following legal action. Healthcare professionals and patients should rely on solid evidence rather than decisions made by regulatory agencies or the judiciary.**

In early 2010, the French *Conseil d'État* (Council of State; the highest administrative jurisdiction) annulled a decision taken by the French drug regulatory agency (Afssaps) that led to the suspension of marketing authorisations for *ketoprofen* gels because of their negative risk-benefit balance (1,2). Thus, a few weeks after their withdrawal in late 2009, most *ketoprofen* gels were back on the French market (3). This article takes a closer look at this unusual and surprising legal decision.

Severe and well documented cutaneous disorders. Many topical non-steroidal antiinflammatory drugs (NSAIDs), such as *ibuprofen* and *diclofenac*, are marketed in France, mainly for mild trauma and rheumatological indications (4,5). *Ketoprofen* gels were first marketed in France in 1989. They are modestly effective, like other NSAID-based gels (6,7), but carry a higher risk of cutaneous disorders (4,7).

A French national pharmacovigilance survey collected 337 spontaneous reports of cutaneous disorders linked to *ketoprofen* gels over a 6-year period, between initial market release and 1995 (4). The cutaneous disorders usually included eczema-like rash and were severe in nearly half of cases. Exposure to light appeared to be a trigger or aggravating factor (4).

Another survey, conducted by the French drug regulatory agency between 2001 and 2009, collected 371 reports of reactions to *ketoprofen* gels, mainly cutaneous disorders (7). The adverse effects were serious in 62% of cases, nearly half of which were photosensitivity reactions (1,7).

Withdrawn from the French market in late 2009. This survey revealed cross-allergy between *ketoprofen* and

octocrilene, an ingredient present in many sunscreens, personal hygiene products and cosmetics (shower gels, creams, lotions) (2,7). Application of a product containing *octocrilene* by patients with a history of skin reactions to *ketoprofen* gel led to recurrence of the same disorders, without concomitant use of *ketoprofen* gel (2,7).

In view of this cross-allergy between *ketoprofen* and *octocrilene*, the French regulator (Afssaps) issued the following statement: "[in view of] the weak to moderate efficacy (...) [of *ketoprofen* gels] and the existence of alternative treatments, Afssaps considers that the risks associated with *ketoprofen* gels outweigh their expected benefits (...)" (2,7). Afssaps suspended marketing authorisation for *ketoprofen* gels, and proceeded to withdraw these products from the market in December 2009 (2,7).

This decision triggered a European reassessment of the adverse effects of *ketoprofen* gels whose conclusions had not yet been released as of 9 April 2010 (2,7,8).

Back on the market again in early 2010, following legal action. After Afssaps suspended marketing authorisation for *ketoprofen* gels, Menarini, a company marketing one of these gels (Ketum^o) applied to the French Council of State for a petition to cancel the suspension in early 2010 (8).

This procedure consists of an emergency action in which a judge makes a provisional ruling on litigation (9,10). It has no bearing on the legality of the underlying issue and is not binding on the court eventually called upon to make a definitive judgement (9,10).

In this case, the judge who issued the injunction concluded (our translation): "(...) that the adverse effect on which this litigation is based only involves about 30 cases, whereas several million units of *ketoprofen* gel are sold each year; (...) that the co-rapporteur designated by the European authorities to examine the French request considers that the risk-benefit balance of *ketoprofen* gel is unchanged; that none of the 20 member states consulted envisages withdrawing this drug; (...) that Ketum (...) yields [for the company, Menarini] a larger profit margin that

the other products it markets, meaning that its withdrawal might compromise the ability of this company to make a profit in fiscal year 2010; thus, the evidence produced by the applicant as to the possible impact of this measure on its activity raises a sufficiently serious and immediate threat to its situation to constitute an emergency; while Afssaps considers that, on the contrary, execution of its decision constitutes a public health emergency, this circumstance does not appear sufficient to stand in the way of meeting the criteria to be deemed an emergency (...)" (8).

Based on these arguments, the judge suspended execution of Afssaps' decision, pending a definitive ruling by the Council of State (2).

Thus, in early 2010, Ketum^o gel was back on the French market (3). In the wake of this decision, other companies also obtained a suspension of Afssaps' decision in order to reintroduce their *ketoprofen* gels to the market (11).

A late but welcome decision by Afssaps. Most adverse drug effects are vastly under-reported by healthcare professionals (12).

For example, the estimated incidence of visual field disorders linked to *vigabatrin* was about 1 per 1000 patients on the basis of spontaneous reports. But, in reality, it is closer to 400 cases per 1000 patients, according to a study focusing specifically on this adverse effect (13). A French survey of paediatricians and general practitioners showed similar under-reporting of local adverse effects associated with the BCG SSI^o vaccine: only 6% of physicians who observed adverse effects actually reported them (14).

The incidence of cutaneous disorders associated with *ketoprofen* gels is certainly far higher than the rate based on spontaneous reports to Afssaps. Regulatory agencies have a clear responsibility to protect public health. However, they are often distracted by issues other than patients' interests, such as the financial health of the pharmaceutical industry (15).

Afssaps' decision to withdraw *ketoprofen* gels from the market was late in coming but more than welcome.



A drug's
real name
INTERNATIONAL NONPROPRIETARY NAME

COMMON STEMS

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In practice: rely on solid data. There has long been evidence that *ketoprofen* gels are more harmful than beneficial in patients with mild disorders. These products carry a risk of frequent and potentially severe cutaneous disorders but have only modest efficacy, at best. When a topical NSAID is indicated, it is better to choose *ibuprofen* or *diclofenac* which cause fewer cutaneous disorders than *ketoprofen*.

One lesson to be learned from this case is that patients and healthcare professionals should base their decisions on solid, relevant and independent data rather than relying on decisions made by regulatory agencies or the judiciary.

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Selected references from Prescrire's literature search.

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- 4- Prescrire Editorial Staff "Cutaneous reaction to topical NSAIDs" *Prescrire Int* 2000; **9** (48): 114-115.
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-mab

The international nonproprietary names (INNs) of monoclonal antibodies end in **-mab** (1,2).

As of 20 March 2010, the World Health Organization (WHO) list of INNs included 156 drugs of this type (3). Substems have been created to make the INNs of monoclonal antibodies more explicit. WHO regularly reviews the nomenclature used to develop INNs for monoclonal antibodies (1,2). The reviews of two monoclonal antibodies in this issue provide the opportunity to take another look at the system used to assign INNs to monoclonal antibodies (4,5,6).

One substem refers to the origin of the antibody: **a** for rat, **axo** for rat/mouse hybrid antibodies; **e** for hamster; **i** for primate; **o** for mouse; **u** for human; **xi** for chimeric antibodies; and **zu** for humanised antibodies (**a**)(1,2).

Another substem indicates the intended use of the monoclonal antibody: **-b(a)-** for antibacterials; **-c(i)-** for a cardiovascular target; **-f(u)-** for antifungals; **-k(i)-** for interleukins; **-l(i)-** for immunomodulators; **-s(o)-** for a bone target; **-tox(a)-** for a toxin target; **-t(u)-** for a tumour target; **-v(i)-** for antivirals (2).

For example, the INN *catumaxomab* refers to a monoclonal antibody (**mab**) of rat and mouse origin (**axo**) that is used in oncology (**tu**) (to treat malignant ascites). The INN *ofatumumab* discussed on page 201 of this issue refers to a monoclonal antibody (**mab**) of human origin (**u**) used in oncology (**tu**) to treat chronic lymphoid leukaemia.

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a- Chimera formation (combining antibody fragments from different species) is a technique used to humanise an antibody of animal origin (ref 4).

Selected references from Prescrire's literature search.

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-ermin (continued)

The international nonproprietary names (INNs) of growth factors end in **-ermin** (1,2). One or more letters are added before this stem to identify the type of growth factor concerned.

Since we first presented this stem in 2006, the World Health Organization (WHO) list of INNs for growth factors has grown from 18 to 25 drugs of this type as of early 2010 (2,3). The following is a summary of the nomenclature used to distinguish between the different types of growth factors included in this vast group.

The stem **-fermin** is used for fibroblast growth factors (1). One such drug, *palifermin*, is marketed in France for the prevention of oral mucositis.

The stem **-nermin** designates a tumour necrosis factor (TNF) (1). One such drug, *tasonermin*, is marketed in France for soft tissue sarcoma of the limbs.

The stem **-otermin** is used for bone growth factors (1). Two of these drugs, *diboterminalfa* and *eptoterminalfa*, are marketed in France for use in orthopaedic surgery.

The stem **-plermin** refers to a platelet-derived growth factor (1). One such drug, *becaplermin*, is marketed in France for certain ulcerated lesions in diabetic patients.

The stem **-sermin** denotes an insulin-like growth factor (1). One such drug, *mecaserminalfa*, is marketed in France for treatment of certain types of growth failure in children and adolescents.

The following stems are used to designate other types of growth factors, but none of these drugs was marketed in France as of early 2010: the stem **-bermin** for vascular endothelial growth factors, the stem **-dermin** for epidermal growth factors, the stem **-filermin** for human leukaemia inhibitory factors, and the stem **-termin** for transforming growth factors (1).

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Selected references from Prescrire's literature search.

- 1- World Health Organization "The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances" WHO/EMP/QSM/2009.3: 84-85.
- 2- Prescrire Rédaction "Le segment-clé du mois -ermine" *Rev Prescrire* 2006; **26** (269): 106.
- 3- "Substances names ending with ermin" mednet.who.int accessed 26 February 2010: 2 pages.