**New Products**

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**ketoprofen gels**

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**Withdrawn from the French market in late 2009.** This survey revealed cross-allergy between ketoprofen and octocrilene, an ingredient present in many sunscreens,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°) 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 than 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° 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° 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.
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.