

Drugs that should not be used: swifter action required to protect patients

This fifth edition of our annual review "Towards better patient care: drugs to avoid" provides an opportunity to examine the decisions taken in France by regulators and pharmaceutical companies to protect patients from these drugs.

Various measures available. Regulators can decide to withdraw or suspend a drug's marketing authorisation, remove it from the list of drugs that qualify for reimbursement by the national health insurance system, or reduce the percentage of its cost that is reimbursed. Pharmaceutical companies can decide to stop marketing a product.

Various combinations of these measures have been applied between 2013 and 2016, each to only a handful of drugs, some of which are discussed below.

Marketing authorisations suspended or withdrawn for about 10 drugs, and some half-measures. *Prescrire's* five annual reviews during this period have identified about a hundred drugs to avoid, but only about ten have been withdrawn from the market through suspension or withdrawal of the marketing authorisations for products containing them. The French Health Products Agency (ANSM) has taken such action far more frequently than the European Medicines Agency.

A number of long-marketed drugs had their marketing authorisations suspended in 2013: products containing *meprobamate* (*Prescrire Int* n° 148) and 5 ergot derivatives (*Rev Prescrire* n° 364).

The marketing authorisation for *indoramin* was withdrawn in 2013, after 28 years on the market (*Rev Prescrire* n° 356) (1). The marketing authorisation for *fioclofenine* was revoked in 2015, after 40 years on the market (*Rev Prescrire* n° 321, 384) (1,2).

Marketing authorisation for *domperidone* 20 mg was withdrawn in 2014, after years of procedures (*Prescrire Int* n° 175). But the 10-mg strength, authorised in France since 1980, remains on the market (1).

A few market withdrawals by pharmaceutical companies. A *theodrenaline* + *cafedrine* combination and *nimesulide* were withdrawn from the market in 2013 (*Prescrire Int* n° 147, *Rev Prescrire* n° 364). In 2014, a *quinine*-containing suppository for cramps was also withdrawn (*Rev Prescrire* n° 377). Their French marketing authorisations therefore became null and void (1).

Quinine Vitamine C Grand° (*Rev Prescrire* n° 400) has not been marketed since 2014, but its French marketing authorisation, granted in 1997, remains valid, and other oral *quinine*-containing products for cramps are still available.

In 2016, the European marketing authorisation for *pegloticase*, granted in 2013, was withdrawn when the company stopped marketing it (*Prescrire Int* n° 180).

Iron dextran ceased to be marketed in France in 2015 (*Rev Prescrire* n° 349; *Prescrire Int* n° 151). Its European

marketing authorisation, granted in 2007, remains valid (1). The same is true of *asenapine*, a neuroleptic authorised in 2010 (*Rev Prescrire* n° 388) (1).

Delisting: a slow process, sometimes challenged, sometimes partial. If a drug's marketing authorisation is upheld, particularly at European level, a stopgap measure is to reduce the number of patients exposed to it through delisting, i.e. removal from the list of products that qualify for reimbursement by the French health insurance system. A number of *trimetazidine*-containing products, including copies, are still available in early 2017 despite being delisted in 2012, suggesting that significant quantities are still sold (*Rev Prescrire* n° 342). *Strontium ranelate* remained available in early 2017 despite being delisted in 2015 (*Rev Prescrire* n° 377).

Some delisting decisions have been challenged in court by the pharmaceutical companies, as was the case for *ketoprofen gel* (*Prescrire Int* n° 109, 112; *Rev Prescrire* n° 317), *diacerein*, *glucosamine* and *olmesartan* (*Rev Prescrire* n° 395, 380). The French health minister has asked for a "treatment protocol" to be drawn up before considering delisting the 4 drugs for Alzheimer's disease (*Rev Prescrire* n° 398) (3).

Sometimes a drug is delisted for certain authorised indications, while other authorised indications are reimbursed at a reduced rate. For example, topical *tacrolimus* was granted European marketing authorisation in 2002, then in 2014 its reimbursement by the French health insurance system was revoked for children and reduced for adults (*Rev Prescrire* n° 245, 367).

Sometimes reimbursement is reduced to 15% of the product's cost, which was the case in 2016 for *agomelatine*, authorised since 2009 (*Rev Prescrire* n° 397).

Mifamurtide and *vernakalant* obtained European marketing authorisations years ago but are not on sale in France, perhaps due to the unfavourable opinion issued by the committee responsible for recommending whether new drugs should be funded by the national health insurance system (see inset p. 110).

In summary: do not wait for companies or regulators to act. The actions taken from 2013 to 2016 by regulators and pharmaceutical companies to rid the market of drugs that are more dangerous than beneficial have been slow and piecemeal, especially at European level.

It is in patients' and health professionals' interests to take matters into their own hands by avoiding these drugs now.

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1- ANSM "Répertoire des spécialités pharmaceutiques". <http://agence-prd.ansm.sante.fr/php/ecodex/> accessed 6 January 2017.

2- HAS - Commission de la transparence "Avis-Idarac" 15 November 2006.

3- Agence France Presse "Médicaments anti-Alzheimer: Touraine écarte le "dérémboursement"" 26 October 2016. www.leparisien.fr accessed 6 January 2017: 3fipages.