Drugs best avoided yet still on the market in early 2012

Many drugs that have more harms than benefits are still marketed in France, and in some cases, for several decades. The following drugs were examined in *Prescrire* in 2011, in order of publication:
– *nimesulide*, a nonsteroidal anti-inflammatory drug (NSAID), because of the risk of liver damage (*Prescrire Int* n° 116);
– antihistamine antitussives, because of their sedative and antimuscarinic effects (issue 329 p. 179);
– *dronedarone*, an antiarrhythmic drug, due to a risk of liver damage and cardiovascular disorders (*Prescrire Int* n° 122);
– terpenes, due to their neuropsychiatric adverse effects (including seizures), especially in young children. In 2011, some medicines for children, mainly suppositories, still contained terpenes. In late 2011, the French drug regulatory agency contraindicated their use in suppositories for children under 30 months (*Rev Prescrire* n° 340);
– *trimetazidine*, marketed for angina, dizziness, visual disorders and tinnitus, carries a risk of extrapyramidal disorders, falls and thrombocytopenia (*Prescrire Int* n° 115). In 2011, the French regulatory agency triggered a referral to the European Medicines Agency;
– *pholcodine*, an opioid antitussive, because of concerns over a risk of allergy to muscle relaxants used during anaesthesia (*Rev Prescrire* n° 331). In 2011, the French agency simply ruled that this drug should be available by prescription only, in order to limit its use (*Rev Prescrire* n° 333);
– oral and nasal vasoconstrictive decongestants (*ephedrine, naphazoline, oxymetazoline, phenylephrine, pseudoephedrine* and *tuaminoheptane*), because of a risk of life-threatening cardiovascular disorders (myocardial infarction, arrhythmia, hypertension). In 2011, the French agency simply demanded a modification in the Summary of Products Characteristics (SPC) (*Rev Prescrire* n° 335);
– *iron dextran*, due to a higher risk of hypersensitivity than with *iron sucrose* (*Rev Prescrire* n° 335);
– *meprobamate* is still contained in certain products in France (for gastrointestinal disorders associated with anxiety, and premenstrual syndrome), despite a risk of severe cutaneous and haematological adverse reactions, and a withdrawal syndrome (*Prescrire Int* n° 123);
– *bupropion*, an amphetamine derivative, and *varenicline*, an acetylcholine receptor partial agonist used for smoking cessation, mainly because of cardiovascular and neuropsychiatric disorders (*Rev Prescrire* n° 329, *Prescrire Int* n° 124);
– *quinine* for cramps, because of a risk of haematological disorders, cardiac arrhythmia and hypersensitivity (*Prescrire Int* n° 115);
– *mequitazine*, a "sedative" and "atropinic" antihistamine used in allergies, carries a higher risk of cardiac arrhythmia than other antihistamines. In 2011, the French agency simply placed *mequitazine* on the list of controlled substances (*Rev Prescrire* n° 337)
– *ropinirole*, a dopamine agonist used for restless legs syndrome (*Prescrire Int* n° 115);
– *orlistat* for weight loss: its adverse effects and interactions largely outweigh a marginal and transient weight loss (*Rev Prescrire* n° 338);

Since late 2011, some of these products are no longer reimbursed in France, including those based on *dronedarone*, *nimesulide* and *quinine* (for cramps). While the measures limit the consumption of these drugs and, thus, the number of patients exposed, they send a mixed message to patients. Simply withdrawing them from the market is the most effective solution.

► – *mesalazine* for children with inflammatory bowel disease, although the packaging is not suitable for all children (*Prescrire Int* n° 119);
– oral *pegylated vitamin E* (*tocofersolan*) avoids the need for painful injections of *vitamin E* (*Rev Prescrire* n° 333).

Some other drugs approved for children provide minor advantages:
– oral *bosentan* solution for pulmonary arterial hypertension (*Rev Prescrire* n° 329);
– *latanaprost* (after beta-blocker eye drops) for ocular hypertension (*Rev Prescrire* n° 333);
– oral suspension of *losartan* for hypertension, but the packaging represents a potential source of errors, the drug is expensive, and access is restricted (*Rev Prescrire* n° 329); and *valsartan* ready-to-use oral solution, reimbursed (the standard angiotensin II receptor blocker for children in 2011) (*Rev Prescrire* n° 327, n° 338).

Orphan drugs: in decline. According to European regulations, "orphan drug" status is granted by the European Commission for medications aimed at treating patients with rare diseases, based on the opinion of the European Medicines Agency (EMA). Drug companies that develop and market such products enjoy certain advantages, including market exclusivity. None of the 6 orphan drugs examined by *Prescrire* in 2011 represented a real breakthrough.

Generic drugs with uneven therapeutic value. In 2011, *Prescrire* examined the harm-benefit balance of 27 generic drugs marketed in France.

Ten of these drugs are useful in certain situations: intradural *baclofen* for some cases of severe chronic spasticity (*Rev Prescrire* n° 332); *clobetasol*, a potent topical corticosteroid for some skin conditions (*Rev Prescrire* n° 328); *dacarbazine* for some cancers (*Rev Prescrire* n° 330); *epoprostenol* for pulmonary arterial hypertension (*Rev Prescrire* n° 328); *letrozole* in breast cancer (*Rev Prescrire* n° 333); *levetiracetam* for various forms of epilepsy (*Rev Prescrire* n° 336); *meropenem* (*Rev Prescrire* n° 337) and *teicoplanin* in severe infections (*Rev Prescrire* n° 331), *modafinil* for narcolepsy (*Rev Prescrire* n° 329); and *valsartan* (with or without *hydrochlorothiazide*) for hypertension, heart failure and recent myocardial infarction (*Rev Prescrire* n° 336).

Many other generic drugs are best avoided, including *milnacipran* in severe depression (*Rev Prescrire* n° 338), *nicorandil* in angina pectoris (*Rev Prescrire* n° 33), and *rivastigmine* in Alzheimer's disease and in dementia associated with Parkinson's disease (*Rev Prescrire* n° 337).

Marketing applications for generic drugs give regulatory agencies an opportunity to reassess the value of the originator drugs, and to withdraw those with a negative harm-benefit balance. Apparently they are not taking advantage of this opportunity.

Patient protection

In 2011, the French health authorities finally started to react, by protecting patients from several drugs that have more harms than benefits (*see* page 110).

Market withdrawals: the most effective measure, often taken late. Drug reassessment can result in measures that support patients' interests, such as market withdrawal of drugs with a negative harm-benefit balance.

In 2011, the French drug regulatory agency finally started to withdraw some of these products, many of which had been on the market for decades:
– *buflomedil*, a vasodilator marketed for over 30 years (*Rev Prescrire* n° 327, n° 329);
– the fixed-dose combination of *clorazepate* + *acepromazine* + *aceprometazine*, available for nearly 40 years in insomnia (*Rev Prescrire* n° 335);
– oral *ketoconazole*, an antifungal drug that can cause severe liver damage (*Rev Prescrire* n° 335);