

New drugs and indications in 2012

Sluggish progress, timid measures to protect patients



Abstract

- The therapeutic advances identified in 2012 were minimal, and 15 new drugs or indications are dangerous.
- The dearth of improvement in patient care contrasts with the sometimes disproportionately high prices agreed upon for drugs, especially in oncology.
- The few steps taken by health authorities that benefited patients, mainly by withdrawing or revoking reimbursement for drugs with an unfavourable harm-benefit balance, were insufficient in view of the constant pressure from the pharmaceutical industry to sell ever more drugs.

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*P*rescrire published systematic reviews of 278 new products and indications in its French edition in 2012, including 34 new products with new brand names, 30 new indications for existing products, generics, line extensions, changes in labelling, name and composition.

The pharmaceutical market overrun with "innovations" that do not represent progress

Continuing the trend observed in previous years, few of the new products and indications we reviewed in 2012 represented a significant advance for patients: only 4 drugs enable healthcare professionals to provide better patient care, one of which has been on the market for some years but was reviewed in 2012 after more follow-up (see table on page 106). Most of the 18 advances identified were slight and do not substantially change prescribing habits: 14 were rated "possibly helpful". See *Prescrire* ratings page 93.

The harm-benefit balance of 7 other new products or indications could not be determined due to insufficient data (rated

"judgement reserved"). Most of these involve treatment of rare diseases and metastatic melanoma (see the table on page 106).

One in five "innovations" best avoided. Half of the new drugs or indications offer no advantages over existing treatments: 42 out of the 82 were rated "nothing new". Year after year, many new drugs are launched that have no demonstrated advantages over the options already available. And some are shown to be dangerous after they have been in use for a few years.

Even more troubling, the proportion of new products and indications with an unfavourable harm-benefit balance remained high in 2012: 15 out of 82 (about 18%) were rated "not acceptable". These drugs, which should never have been authorised in these indications, join a long list of existing drugs that the health authorities should already have withdrawn, sometimes many years ago (see pages 108-111).

Drug prices continue to rise. When pharmaceutical companies launch new drugs, they seek to secure increasingly high sales prices from governmental agencies (*Prescrire Int* n° 129). Oncology is one of the fields in which expenditure for drugs has reached disproportionate levels in France: about €3600 per month for *abiraterone* in metastatic prostate cancer (*Prescrire Int* n° 128); about €4400 per month for *dasatinib* in certain leukaemias (*Prescrire Int* n° 123); about €2900 € to 4100 per month for *everolimus* in pancreatic neuroendocrine tumours (*Prescrire Int* n° 131). Another example is *pirfenidone* for idiopathic pulmonary fibrosis, which although its harms outweigh its benefits, costs about €2120 per month (see May 2013 issue).

The cost of these drugs bears no relation to the progress they represent.

Sustained-release *quetiapine*, for example, costs 10 to 20 times more than standard treatments, despite having no demonstrated advantages; meanwhile, society pays for the promotion of this expensive neuroleptic (*Rev Prescrire* n° 339).



Prescrire's ratings of new products and indications over the last 10 years (a)

Prescrire's rating	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Bravo	0	0	0	1	1	0	0	0	0	0
A real advance	4	0	1	1	2	0	0	1	0	1 (b)
Offers an advantage	5	6	4	8	14	6	3	3	3	3 (c)
Possibly helpful	23	12	20	31	27	25	14	22	13	14
Nothing new	34	41	38	69	79	57	62	49	53	42
Not acceptable	7 (d)	7	19	17	15	23	19	19	16	15 (e)
Judgement reserved	6	4	2	8	3	9	6	3	7	7 (f)
Total	79	70	84	135	141	120	104	97	92	82

a- The previous years' results (1988 to 2002) can be found in *Prescrire* Int n° 64. This table lists new products (other than generics) and new indications (including unauthorised indications) proposed in France by drug companies to doctors and pharmacists, for use in hospitals or the community; and, as of 2005, line extensions (new dose strengths, new formulations and presentations) of existing drugs and products for self-medication, rated in our French edition, *la revue Prescrire*. A given product is counted several times if it received different ratings in different indications.

b- The drug was: boceprevir in chronic hepatitis C (*Prescrire* Int n° 126).

c- The drugs were:

– abiraterone in prostate cancer after failure of other treatments (*Prescrire* Int n° 128);

– telaprevir in chronic hepatitis C (*Prescrire* Int n° 126);

– trastuzumab as adjuvant therapy for breast cancer after more follow-up (*Prescrire* Int n° 133).

d- Including two jointly marketed products.

e- The drugs were:

– asenapine in manic episodes in bipolar disorder (*Prescrire* Int n° 131);

– bevacizumab in metastatic breast cancer in combination with capecitabine (*Rev Prescrire* n° 340);

– bevacizumab in advanced ovarian cancer (*Rev Prescrire* n° 348);

– domperidone in gastrointestinal disturbances (*Rev Prescrire* n° 340);

– fluticasone in atopic dermatitis in infants 3 months of age and older (*Prescrire* Int n° 129);

– insulin detemir in combination with liraglutide in type 2 diabetes (*Rev Prescrire* n° 348);

– ivabradine in heart failure (*Rev Prescrire* n° 348);

– linagliptin in type 2 diabetes (*Rev Prescrire* n° 347);

– pirfenidone in mild to moderate idiopathic pulmonary fibrosis (*Rev Prescrire* n° 350);

– roflumilast in severe chronic obstructive pulmonary disease (*Prescrire* Int n° 134);

– saxagliptin in type 2 diabetes in combination with insulin (*Rev Prescrire* n° 349);

– the saxagliptin + metformin combination in type 2 diabetes (*Rev Prescrire* n° 349);

– sildenafil in pulmonary arterial hypertension in children (*Prescrire* Int n° 129);

– vandetanib in medullary thyroid cancer (*Prescrire* Int n° 131);

– vernakalant in atrial fibrillation (*Prescrire* Int n° 127).

f- The drugs were:

– carglumic acid for organic acidaemia in neonates and infants (*Rev Prescrire* n° 349);

– brentuximab vedotin in Hodgkin's lymphoma or systemic anaplastic large cell lymphoma (*Rev Prescrire* n° 349);

– ipilimumab in metastatic melanoma (*Prescrire* Int n° 128);

– mexiletine in myotonic syndromes (*Rev Prescrire* n° 344);

– ranibizumab in retinal vein occlusion (*Prescrire* Int n° 130);

– tafamidis in transthyretin amyloidosis (*Rev Prescrire* n° 349);

– vemurafenib in metastatic melanoma (*Prescrire* Int n° 133).

► **Little publicity surrounding drug safety withdrawals.** While new drugs are often announced amid much fanfare, market withdrawals tend to receive little publicity.

Pharmaceutical companies and drug regulatory agencies sometimes present patients and healthcare professionals with a fait accompli. In 2012, some products that are still quite useful were withdrawn for economic reasons, including: injectable *fusidic acid*, one option in certain staphylococcal infections (*Rev Prescrire* n° 347); and *lepirudin*, which was an alternative to *danaparoid* before market release of *argatroban* (*Rev Prescrire* n° 348). On occasion, healthcare professionals and patients even have to fight to keep a product on the market, as was the case for Phosphoneuros®, an oral solution containing *phosphate*, which is useful for certain children with hypophosphataemic rickets (*Rev Prescrire* n° 348).

A few measures to protect patients

One key responsibility of governmental agencies is to protect patients. They have a number of measures at their disposal to oversee and regulate the pharmaceutical market, in order to ensure that patients are not exposed to unnecessary risks.

Market withdrawal, MA rejection, MA revocation: too rare. Market withdrawal and the revocation, restriction or rejection of a drug's marketing authorisation (MA) are effective measures for protecting patients, but are still too rarely used.

A few decisions were taken in 2012 that reflect a trend towards patient protection: suppositories containing terpenes were contraindicated in children under 30 months of age, due to the risk of seizures (*Rev Prescrire* n° 340); the neuroleptic *metoclopramide*, which is approved to relieve nausea and vomiting, was contraindicated in children due to its disproportionate neurological adverse effects, and a *metoclopramide* oral solution for infants and children was subsequently withdrawn from the French market (*Rev Prescrire* n° 345 and 340).

In 2012, *Prescrire* welcomed a few unfavourable opinions issued by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP), concerning: *naproxenod*, a non-steroidal anti-inflammatory drug that exposes patients to disturbing risks of hypotension and hepatotoxicity (*Prescrire* Int n° 129); and *sodium oxybate* in fibromyalgia, which provokes major dose-dependent neuropsychiatric adverse effects (*Prescrire* Int n° 133).

The French Transparency Committee fulfilling its role. In France, the National Authority for Health's (HAS) Transparency Committee is responsible for evaluating the therapeutic benefit (*Service Médical Rendu*) of drugs, especially those for which pharmaceutical companies have applied for reimbursement by the national health insurance system or approval for use in hospitals. When a product's therapeutic benefit is deemed "insufficient", reimbursement must be refused or revoked: a welcome development. But often, it is a stopgap measure that simply reduces the number of patients exposed to a dangerous drug that should not remain on the market.

In 2012, reimbursement for several drugs with unacceptable risks was revoked, including: certain combinations of vasoconstrictors used as decongestants, but not *naphazoline* + *prednisolone* (*Rev Prescrire* n° 350); *dronedarone* in atrial fibrillation; *beta-alanine* in hot flushes associated with menopause; *ropinirole* in restless legs syndrome; *trimetazidine* in angina and various sensory disturbances; and "vasodilators" in age-related neurosensory cognitive deficits (*Rev Prescrire* n° 339, 342, 345 and 348).

Information about the risks of drugs: easily missed. Apart from a few announcements issued by health authorities, new information published by regulatory agencies about the risks of

drugs is easily missed. *Prescrire* carefully reads all of the changes made to summaries of product characteristics (SPCs), as well as all the published minutes of the meetings of regulatory agency committees, in order to identify any new information that would be useful in healthcare practice or for patient protection.

A few notable examples unearthed in 2012 are: hepatic risks and hallucinations added to the SPC for *agomelatine* (*Rev Prescrire* n° 348); optic neuropathy reported in the EMA's "Procedural steps taken and scientific information after the authorisation" for *bortezomib* (*Rev Prescrire* n° 349); serious, including fatal, skin lesions added to the SPC for *febuxostat* (*Rev Prescrire* n° 347); abuse and addiction associated with *methylphenidate*, an amphetamine-like stimulant marketed for attention-deficit hyperactivity disorder, reported in the minutes of a French drug regulatory agency (ANSM) meeting (*Rev Prescrire* n° 344); deaths and cutaneous and cardiac risks associated with *midodrine*, reported in the minutes of an ANSM meeting (*Rev Prescrire* n° 343); and occasionally serious allergic reactions added to the SPC for *Saccharomyces boulardii*, a probiotic taken for diarrhoea (*Rev Prescrire* n° 348).

Advertising and marketing: the authorities are too lenient

Drug companies use various strategies to encourage drug consumption. Healthcare professionals and patients cannot rely on the information they provide, given their major conflicts of interest.

In 2012, we exposed several tactics used by pharmaceutical companies that place profits above patients' needs: proposing a pharmacological solution to all health problems (medicalisation of life and disease mongering); using opinion leaders to influence healthcare professionals; and funding "training" for medical students (*Rev Prescrire* n° 339, 341 and 349).

Some companies have engaged in truly harmful activities, for example: Roche concealed adverse effects, particularly in patients who had died; and GlaxoSmithKline conducted misleading promotional campaigns encouraging off-label use of its drugs (*Rev Prescrire* n° 349).

In France, in 2012, before prior approval was required for drug advertising aimed at health professionals, 7 advertisements were banned for serious violations: unethical extension of indications, exaggeration of efficacy, or promotion of off-label use. One of these ads promoted the use of the nonsteroidal anti-inflam-

Drug policy: let's maintain pressure on regulatory authorities

France's recent "drug safety" law, developed in response to the Mediator® (*benfluorex*) disaster, was supposed to ensure that greater consideration would be given to the dangers of drugs (*Prescrire Int* n° 127). In practice, the law passed at the end of 2011 fell well short of the initial recommendations.

Some progress in transparency. The French health products agency's (ANSM) resolve to oversee and regulate medicinal products has remained timid, although progress initiated at the end of 2011 with the publication of the agendas and detailed minutes of its committees' meetings continued in 2012.

Prescrire has also noted that the French National Authority for Health (HAS) provides slightly more information on its website, having published 2 draft opinions on drugs for which the pharmaceutical company withdrew its request for reimbursement (*Rev Prescrire* n° 350).

However, experience has shown that some opacity remains.

No bold political decisions in 2012. Commitment has faded since policymakers took a bold stance during debates on France's "drug safety" bill. No significant progress was made in 2012.

A number of measures are still required if drug policy is to better serve the interests of patients and all citizens:

- a significant increase in the funding of independent clinical research, free from the influence of the pharmaceutical industry (*Prescrire Int* n° 129);
- a body of independent experts with no vested interests;
- changes in European legislation, making it mandatory to compare new drugs with standard treatments to determine the therapeutic advance they represent (*Rev Prescrire* n° 342);
- establishment of an evidence-based hierarchy of treatment options;
- high-quality, safe drug packaging, to prevent medication errors (see the May 2013 issue);
- greater transparency on the part of health authorities, including access to clinical trial data and pharmacovigilance data;
- funding for continuing education for healthcare professionals, free from the influence of the pharmaceutical industry;
- the exclusion of commercial interests from all healthcare and educational establishments;
- improved detection and compensation of victims of the adverse drug effects.

Consider patients first. Given the weaknesses in drug regulation in both France and the European Union, it is up to healthcare professionals to be critical and to always put patients' interests first.

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matory drug *flurbiprofen* during pregnancy, which could harm the unborn child (*Rev Prescrire* n° 340, 342 and 347).

Drug advertising is bad for health, yet the authorities continue to refuse to ban it. In France, in 2012, a small breakthrough was made by requiring prior authorisation of drug advertisements aimed at health professionals (*Rev Prescrire* n° 347). On the other hand, governmental agencies missed an opportunity to put an end to direct-to-consumer advertising of vaccines (*Rev Prescrire* n° 350).

All too often, the drug industry's interests continue to take precedence over those of patients and public health.

Putting patients' interests first

In 2012, yet again, any true therapeutic advances were minimal, and did not reverse the trend observed in previous years, leading to the 2011 *Prescrire* Drug

Awards ceremony in which not a single medication was granted an award (*Prescrire Int* n° 125).

The pharmaceutical market is still overrun with dangerous drugs: we have drawn up a list, based on 3 years of *Prescrire* reviews, that includes about 80 drugs that should not be prescribed, without waiting for regulatory action (see pages 108-111). The health authorities do not fully appreciate the dangers of these drugs. Regulatory agencies can no longer afford to simply inform patients of the risks or to procrastinate: it is high time these drugs were withdrawn from the market.

Let's hope that 2013 will be the year of major advances in patient protection.

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