New drugs and indications in 2010: inadequate assessment; patients at risk

In 2010, we rated 97 new drugs or new indications in our French edition la revue Prescrire, only 4 of which provided a therapeutic advantage. However, 19 others (1 in 5) were approved despite having more harms than benefits.

More paediatric products were released in 2010 than in previous years, but few of them made any real difference and many had not been properly evaluated.

Drug regulatory agencies can protect patients from exposure to dangerous drugs by refusing to grant market approval or by demanding their market withdrawal. Yet they are failing to fulfil this responsibility: so-called risk management plans and modifications to the wording in the SPC are only half-measures.

Too often the authorities put companies’ short-term financial interests above patients’ well-being by granting premature marketing authorisation, by agreeing to high levels of reimbursement that fail to take added therapeutic value into account, and by allowing the development of “umbrella” ranges.

The European authorities’ questionable plans for pharmacovigilance and advertising of prescription-only drugs were restricted after public mobilisation, but they are still likely to undermine healthcare quality.

Decision-makers must make patients’ well-being their top priority.

In 2010, our independent analyses of 291 new drugs and indications were published in our French edition la revue Prescrire. They included: 46 new products with new brand names, 17 line extensions, and 24 copies with fancy brand names (“hidden generics”) (a).

All that glitters...

We systematically examine the therapeutic value of all new drugs, products with new brand names, line extensions, and new indications of existing products in France. In 2010, we rated 97 drugs, including 3 products that we re-examined after longer follow-up.

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(a) In addition: new indications, reassessments (“A second look”) for drugs already analysed in Prescrire, generics, wording changes in the labelling, miscellaneous changes, brand name changes, and market withdrawals.
New drugs and indications in 2010

In 2010, certain drugs represented a slight therapeutic advance (rated as “Possibly helpful”), but their assessment was usually minimal and sometimes wholly inadequate. They included:

- darunavir (Rev Prescrire n°321) and tipranavir (Rev Prescrire n°321) for HIV-infected children;
- fosfomycin for hypertensive children (Prescrire Int n°108);
- omepazole in heartburn and gastroeophageal reflux, and Helicobacter pylori infection (Rev Prescrire n°319);
- the combination of peginterferon alfa-2b and ribavirin in hepatitis C (Rev Prescrire n°325);
- botulinum toxin type A for limb spasticity (Rev Prescrire n°325).

Monoclonal antibodies: too many products, rarely helpful. The number of therapeutic monoclonal antibodies (whose international non-proprietary names (INNs) end in -mab) and their indications continue to grow, especially in oncology and rheumatology. These drugs are publicised as “targeted treatments” heralding an era of “personalised medicine”. In practice, they rarely represent a major therapeutic advance, and several expose patients to unjustified risks (see notes d and e of the rating table below).

Outlook

Half of these new products and indications – 49 to be precise – provided no advantages over existing options.

Some conditions, such as cancer, diabetes and hypertension, are particularly lucrative for drug companies, but patients rarely benefit.

Lack of therapeutic advance. In 2010 we found that only 4 drugs provided a therapeutic advantage (see notes c and d of the rating table below). The only drug we rated “A real advance” was imatinib (Prescrire Int n°114), a product that had already been on the market for several years and that we re-evaluated in 2010 (see note c of the rating table below). The new data showed an overall survival time of more than 4 years with imatinib in patients with inoperable or metastatic gastrointestinal stromal tumours, compared to only 1.5 years previously.

Too few data were available to determine the role of 3 other drugs in the therapeutic arsenal (see note f of the table below). One of these 3 drugs was a cell therapy product (autologous chondrocytes, in a coming issue).

Recycling. Incapable of bringing new drugs to the market that represent a real therapeutic advance, companies are recycling old drugs in the form of fixed-dose combinations or new routes of administration. The following are a few examples in the field of cardiology, in which fixed-dose combinations continue to flood the market: amiodipine + valsartan + hydrochlorothiazide (Prescrire Int n°114), a fixed-dose combination of peginterferon alfa-2b and ribavirin (Rev Prescrire n°316), and nevirapin + hydrochlorothiazide (Rev Prescrire n°316).

One in five new products can be avoided. In Prescrire’s at-a-glance rating system, “Not acceptable” indicates that the drug has a negative risk-benefit balance in one or more of its approved indications. The proportion of drugs that we consider “Not acceptable” has been high for the past several years and was about 20% in 2010 (19 out of 97 ratings). Half of the products concerned are cytotoxic agents authorised for use in cancer or haematological disorders (see note e of the rating table below).

Two generic drugs examined in 2010 have negative risk-benefit balances: nefopam in acute, especially postoperative, pain (Rev Prescrire n°324), and oxzemoxine, in cough (Rev Prescrire n°323).

Paediatrics: inadequate assessment and little progress. Since 2007 and the implementation of the European Paediatric Regulation requiring companies to evaluate their drugs in children (unless exempted), the number of drugs authorised for paediatric use has been increasing.

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

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(a) For reasons of space, this table only shows the results for the last 10 years. The previous years’ results (1981 to 2000) can be found in Prescrire Int n°58.

This table shows new products (other than generics copies) and new indications proposed by drug companies to physicians and pharmacists, for use in hospitals and/or the community; and, from 2005 onwards, line extensions (new dose strengths, new forms/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 was rated differently in its different indications.

b Including two jointly marketed products.

c Imatinib reassessed in inoperable or metastatic gastrointestinal stromal tumours (Prescrire Int n°114).

d The drugs were:
- fixed-dose combination of amiodipine + valsartan + hydrochlorothiazide (Prescrire Int n°114);
- bevacizumab in metastatic breast cancer (Rev Prescrire n°317);
- capsaicin patches for neuropathic pain (Rev Prescrire n°318);
- catumaxomab in malignant ascites (Prescrire Int n°109);
- cetuximab in colon cancer (Prescrire Int n°110);
- duloxetine in prevention of recurrent depression (Prescrire Int n°111);
- histamine in acute myeloblastic leukaemia (Rev Prescrire Int n°321);
- ibalbutadine in stable angina (Prescrire Int n°109);
- intravenous in bladder cancer after failure of first-line cisplatin-based treatment (Prescrire Int n°112).

e The drugs were:
- fixed-dose combination of amiodipine + valsartan + hydrochlorothiazide (Prescrire Int n°114);
- bevacizumab in metastatic breast cancer (Rev Prescrire Int n°114);
- omalizumab in severe persistent asthma (Prescrire Int n°324);
- omalizumab in severe persistent asthma, a reassessment (this issue p 90);
- maraviroc in first-line treatment of HIV-infected patients (Prescrire Int n°110);
- milatarmide in osteosarcoma (Rev Prescrire n°326);
- pazopanib in kidney cancer (Prescrire Int n°114);
- sildenaft (Prescrire Int n°109) and tadalaft (Rev Prescrire n°321) in stage II (mild) pulmonary hypertension;
- tiomiltrim in mantle cell lymphoma (Prescrire Int n°111);
- trastuzamab in oestrogen receptor-positive breast cancer (Rev Prescrire n°326);
- vinflunine in bladder cancer after failure of first-line cisplatin-based treatment (Prescrire Int n°112).

f The drugs were:
- autologous chondrocytes in autologous chondrocyte grafting for knee cartilage damage (Rev Prescrire n°326);
- imatinib as an adjuvant to surgical excision of gastrointestinal stromal tumours (Prescrire Int n°113);
- saptroproin in tetrabiopterin deficiency (Rev Prescrire n°316).
Avoiding iatrogenic complications

Marketing authorisation is being granted prematurely for an increasing number of new drugs, before their efficacy and particularly, their adverse effects have been properly evaluated (Rev Prescrire n°326).

One would expect drug regulatory agencies to be more cautious and responsive following scandals such as the diethylstilbestrol (DES) disaster and, more recently, the benfluorex (ex-Mediator®) affair (Prescrire Int n°105, 107, 113 and Prescrire website).

Market withdrawal: an effective measure, especially when timely.

Drug regulatory agencies often appear reluctant to withdraw drugs with negative risk-benefit balances, allowing sales to continue unabated and needlessly exposing patients to a risk of adverse effects.

The return of topical ketoprofen to the market after initial withdrawal at the demand of the French drug agency (Afsaps) illustrates how drug companies’ financial interests are often put ahead of patient safety (Prescrire Int n°109, 112, 113).

In 2010, only a small proportion of drugs with a negative risk-benefit balance were taken off the market, several years after their dangers were first identified. They included bufexamac, a topical nonsteroidal antiinflammatory drug, because of potentially serious cutaneous disorders (eczema) (Rev Prescrire n°321, 325); carboestane and acetylcysteine (mucolytic agents) in infants, because of respiratory adverse effects (Rev Prescrire n°320, 324); rosiglitazone (an antidiabetic drug with potential risks) (Prescrire Int n°109, 112). The French regulator (Afsaps) decided to withdraw these gels in late 2009, but in mid-2010, CHMP recommended that they be allowed to remain on the market; nimesulide because of potentially life-threatening liver damage (Rev Prescrire n°323); celecoxib (Celebrex® in rheumatology, and Onsenal® in familial adenomatous polyposis) and etoricoxib because of an excess of cardiovascular and cutaneous disorders (see www.english.prescrire.org and Prescrire Int n°108); parecoxib because of life-threatening skin reactions (Prescrire Int n°109). And also: meprobamate because of the high risk of adverse effects with this psychotropic drug, too often misused as a “recreation-al” drug (see www.english.prescrire.org); nicorandil because of its unknown efficacy in angina pectoris and the risk of serious ulceration (gastrointestinal, vaginal, etc.) (Prescrire Int n°110); quinine for cramps, because of the risk of potentially life-threatening haematological effects (Rev Prescrire n°326); pioglitazone, an antidiabetic drug with adverse effects that outweigh its efficacy (Rev Prescrire n°325 and www.english.prescrire.org); refusals of extension of the indications for two psychotropics used in fibromyalgia: pregabaline and milnacipran (in depression) (Rev Prescrire n°320).

Adverse effects: insist on more openness.

Because marketing authorisation is increasingly granted prematurely, the adverse effect profiles of many new drugs are not properly documented at the time of market release.

Post-marketing data on adverse effects are therefore crucial and must be made available to the public. The European Medicines Agency (EMA) issued alerts on the following products (among others) in 2010: becaplermin because of infections and cancer (Prescrire Int n°108); fluoxetine because of cardiac malformations in newborns exposed in early pregnancy (Rev Prescrire n°323); lenalidomide because of myocardial infarction (Prescrire Int n°109); olanzapine because of sudden death and urinary incontinence (Prescrire Int n°109); olirsat because of interactions, pancreatic and nephropathies (Prescrire Int n°107, 110); angiotensin II receptor.

Drugs to avoid

The following is a list of certain drugs analysed in Prescrire in 2010 that have more potential harms than benefits and that should be avoided pending the decision by the authorities (or the drug companies) to take them off the market.

NSAIDs, antidiabetics, psychotropics, etc. Several nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, especially cox-2 inhibitors: – topical ketoprofen gel because of cutaneous disorders (Rev Prescrire Int n°109, 112). The French regulator (Afsaps) decided to withdraw these gels in late 2009, but in mid-2010, CHMP recommended that they be allowed to remain on the market; nimesulide because of potentially life-threatening liver damage (Rev Prescrire n°323); – celecoxib (Celebrex® in rheumatology, and Onsenal® in familial adenomatous polyposis) and etoricoxib because of an excess of cardiovascular and cutaneous disorders (see www.english.prescrire.org and Prescrire Int n°108); – parecoxib because of life-threatening skin reactions (Prescrire Int n°109). And also: meprobamate because of the high risk of adverse effects with this psychotropic drug, too often misused as a “recreation-al” drug (see www.english.prescrire.org); nicorandil because of its unknown efficacy in angina pectoris and the risk of serious ulceration (gastrointestinal, vaginal, etc.) (Prescrire Int n°110); quinine for cramps, because of the risk of potentially life-threatening haematological effects (Rev Prescrire n°326); – pioglitazone, an antidiabetic drug with adverse effects that outweigh its efficacy (Rev Prescrire n°325 and www.english.prescrire.org); – ropinivole in restless legs syndrome: this dopamine agonist has known adverse effects but no proven efficacy in this setting. In 2010, the French authorities recommended that it no longer be reimbursed (Rev Prescrire n°325); – telithromycin, a macrolide carrying a risk of cardiac, hepatic and visual disorders (Prescrire Int n°106 and www.english.prescrire.org); – trimetazidine, because of a negative risk-benefit balance in angina pectoris, dizziness, tinnitus and visual disorders, and especially a risk of extrapyramidal syndrome and thrombocytopenia (Prescrire Int n°106 and www.english.prescrire.org).

Cost of inadequate regulation. In view of these few examples, how can decision-makers and health authorities be trusted, when they allow patients to be exposed to harmful drugs, letting society pick up the tab for hospitalisation, sick leave, and agree to provide reimbursement for vastly over-priced drugs.

For example, the direct cost of prescriptions for glitazones in France was about 50 million euros in 2007, for the national health insurance system alone (Rev Prescrire n°317). There is a cost for inadequate regulation. Decision-makers can start to get a grip on health spending by refusing to provide reimbursement for drugs with a negative risk-benefit balance.

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New drugs and indications in 2010

Medicines agencies too often under the influence of drug companies

Drug regulatory agencies are responsible for protecting patients, notably by assessing drugs before they are allowed on to the market. Yet in 2010, the European agency (EMA) and EU member states’ agencies, including the French agency Assaps, often failed to fulfil their responsibilities.

At a broader international level, the norms dictated by ICH (International Conference on Harmonisation) also fail to make patient safety their priority. It is this organisation, composed of representatives from the wealthiest countries’ drug regulatory agencies and 3 drug company trade associations, that sets the rules governing market access for new drugs (Prescrire Int n°108).

When agencies disagree, drug companies benefit. Drug regulatory agencies in various countries sometimes come to different decisions concerning approval of a specific drug: one country might wish to withdraw a risky drug, while others will insist on keeping it on the market. There is no valid reason why this should benefit the company rather than patients. Several such situations arose in 2010.

Rosiglitazone was withdrawn in the European Union but not in the United States, where the authorities simply demanded modifications in the wording of the SPC (Rev Prescrire n°325 and www.english.prescrire.org).

Nimesulide was withdrawn from the market in Argentina, Belgium, Spain, Finland, Ireland, Singapore, etc., but not in all European Union member states. The CHMP even requested a study evaluating the hepatic risks in transplant centres, further delaying the decision on market withdrawal (Rev Prescrire n°323 and www.english.prescrire.org).

Parecoxib was withdrawn from the Swiss market and rejected by the US Food and Drug Administration (FDA), yet it is still authorised in the European Union (Prescrire Int n°109).

Maraviroc has been authorised for first-line treatment of HIV infection in the United States, but not in the European Union, where the authorities justifiably consider that the assessment is inadequate (Prescrire Int n°110).

Agencies still grant marketing authorisation despite inadequate data. Accelerated marketing authorisation based on partial data may be justified when patients have no other treatment options and might reap a major benefit. But drug regulatory agencies increasingly approve new drugs on the basis of scant data, without demanding a comparison with an existing reference treatment. It sometimes seems that marketing authorisation is granted as a consolation prize for companies that have submitted multiple applications in various indications.

Tolvaptan was authorised for the syndrome of inappropriate antidiuretic hormone secretion, with no proof of efficacy, although the company had initially applied for an indication in heart failure (Prescrire Int n°109).

Gefitinib was authorised for some lung cancers on the basis of a minimal analysis showing no increase in survival (Prescrire Int n°107).

After unfavourable opinions issued by the FDA and EMA based on data presented in 2005, the EMA finally authorised dronedarone in atrial fibrillation, despite the lack of convincing data (Prescrire Int n°108).

Trials of raltegravir in first-line treatment of HIV-infected patients were not designed to show a benefit versus effective anti-retroviral combinations (Prescrire Int n°110).

The assessment report on vinflunine in bladder cancer states that the CHMP authorised this drug on the basis of a majority decision with many dissenters (Prescrire Int n°112).

Conflicts of interest: too many experts with ties to drug companies. The French agency contracts outside experts to assess marketing applications. In late 2009, it published a review of how conflicts of interest were handled within the agency. This report revealed that regulatory obligations were not fully respected; in particular, more than half of the experts were not required to leave meetings in which they had a major conflict of interest (Prescrire Int n°108). These findings highlight the need for independent experts.

In 2010, the pharmaceutical industry was still heavily involved at every step of drug evaluation. And the fact that drug regulatory agencies are largely funded by drug companies (to the tune of 80% in the case of the EMA) rules out the likelihood of objective assessment (Rev Prescrire n°319). European citizens must fight for the independence of drug regulatory agencies from the pharmaceutical industry.
Inadequate “risk management” plans. “Risk management” plans and “risk minimisation” measures are frequently inadequate. They are often delegated to drug companies by drug regulatory agencies, and they mainly serve to justify premature marketing authorisation with a commitment to conduct large post-marketing trials (Rev Prescrire n°319).

Heterogeneous “umbrella” ranges: caution

In France, the self-medication market continued to grow in 2010, but most new products had little if any efficacy and did have noteworthy adverse effects. In addition, the fancy brand names and packaging concocted by manufacturers and allowed by drug agencies are unlikely to promote rational use. Pharmacists must carefully select the self-medication products they sell to their clients.

New self-medication products: amorolfine and omeprazole sometimes useful. In 2010, five drugs became available without a prescription: amorolfine (Rev Prescrire n°319), levocabastine (Rev Prescrire n°320), omeprazole (Rev Prescrire n°326), tixocortol (Rev Prescrire n°320) and trimebutine (Rev Prescrire n°326).

Some provide a small benefit:
- amorolfine (Rev Prescrire n°321) is only applied once a week for fungal nail infections, instead of once a day as with ciclopirox;
- omeprazole (Rev Prescrire n°326) is the standard proton pump inhibitor for gastrointestinal reflux.

In contrast, tixocortol, a steroid, should not be used for sore throat (Rev Prescrire n°320).

Fancy brand names and “umbrella” ranges: misinformation and danger. Patient safety can be improved by highlighting the INN on drug labelling or including it in the brand name, thus reducing the risk of overdose with drugs present in several self-medication products, such as paracetamol and ibuprofen. This can also help to avoid confusion between similar brand names (Rev Prescrire n°318, 325).

In practice, the INN is rarely highlighted, particularly in self-medication products. “Umbrella” ranges, in which several products with a different composition or regulatory status share a common stem as part of their brand name, are proliferating. This creates a risk of confusion between drugs belonging to the same product line. This is especially the case for products sold to treat coughs and colds. For example, the following “umbrella” ranges were extended in France in 2010: Clarix® (Rev Prescrire n°318), Codotussyl® (Rev Prescrire n°317), Dolirhume® (Rev Prescrire n°318) and Humex® (Rev Prescrire n°317).

Advertising: drug companies continue to spin their web

In late 2009, after reviewing the activities of medical sales reps, the French National Authority for Health (Haute autorité de santé, HAS) stressed the ineffectiveness of the medical sales charter, and admitted that it was incapable of regulating this activity (Rev Prescrire n°109). Although late in coming, this is a welcome realisation. In the meantime, however, drug companies continue to engage in advertising practices that put patients at risk.

Direct-to-consumer (DTC) advertising of prescription drugs: danger. The European Commission’s plans to allow companies to advertise prescription-only drugs directly to the public were once again debated by the European Parliament in late 2010 (see www.english.prescrire.org). The draft text was largely amended but still leaves too much open for some possible drug company advertising of prescription drugs to the public.

Marketing costs: nearly one-quarter of drug companies’ total spending. Patients and healthcare professionals need reliable and comparative information on illnesses and their management. Drug companies, for which each illness represents a market niche, are not in a good position to meet this need (Rev Prescrire n°324, 326). Yet marketing costs represent about 23% of drug companies’ spending, according to a survey conducted by the European Commission (Rev Prescrire n°315).

Drug promotion can take various forms, from training courses “under the influence” of the private sector (Rev Prescrire n°319), to the use of high-tech gimmickry to hide the dearth of real innovation (Rev Prescrire n°316), and advertising disguised as scientific information (Rev Prescrire n°323). Some healthcare professionals contribute indirectly to drug companies’ marketing strategies by providing information on prescriptions and sales, sometimes in return for small gifts (Rev Prescrire n°315).

Illicit advertising aimed at healthcare professionals. Doctors, pharmacists and even nurses are all targeted by drug companies seeking to increase sales of their products (Rev Prescrire Int n°108).
New drugs and indications in 2010

Finding solutions, along with patients

Faced with ongoing deregulation, with companies overstepping their roles, and with decision makers and health authorities who still fail to make patients’ interests their top priority, it is up to healthcare professionals to assure quality of care and maintain patient trust.

Training and education. Quality healthcare requires continuing education for healthcare professionals and reliable information for patients. This implies:

• basic education for all healthcare professionals in the principles of critical appraisal (Rev Prescrire n°320), so that they are in a position to analyse clinical assessment data on individual drugs, instead of relying solely on others’ judgement (Rev Prescrire n°321); it is particularly important to be able to distinguish surrogate endpoints from robust outcomes that take adverse effects into account (Rev Prescrire n°320);
• searching SPCs for “buried” information such as clinical trial data and adverse effects (Rev Prescrire n°319);
• being able to recognise a drug’s pharmacological class, notably by using international nonproprietary names (INNs), in order to avoid exposing patients to known adverse effects (Prescrire Int n°108);
• reminding patients not to believe everything they read or hear in the media. Reports of research results in the lay media can be misleading; many researchers have a tendency to exaggerate the significance of their findings, both for financial reasons and for personal status (Rev Prescrire n°320);
• acknowledging one’s errors, as part of a constructive attitude towards improving professional practice (Prescrire Int n°109).

Mobilise! The positive impact that healthcare professionals and patients can have on healthcare quality was illustrated by several events in 2010:

• a French physician succeeded in bringing the severe adverse effects of benfluorex (ex-Mediator°) to the public’s attention (Rev Prescrire n°325 and www.english.prescrire.org), and a national health insurer (Cnamts) commissioned a study of its adverse effects (issue 316 p. 114), both of which led to benfluorex being withdrawn from the French market;
• patient groups successfully lobbied for market reinstatement of 100-mg capsules of efavirenz that are adapted to the treatment of certain HIV-infected young children (Rev Prescrire n°320).

Patients first!

In 2010, as in previous years, there was a dearth of real therapeutic advance as well as continued failings of policy makers and healthcare authorities, such as approval of poorly evaluated drugs with negative risk-benefit balances, or failure to withdraw them from the market.

Unable to rely on regulatory agencies and healthcare authorities, it is up to healthcare professionals to select drugs that truly benefit their patients and avoid needlessly exposing them to the risk of adverse effects.

Resist “medicalisation of life”. Disease-mongering continued unabated in 2010, especially in the field of mental health (Rev Prescrire n°321 and www.english.prescrire.org). Thus, in draft version V of the Diagnostic and Statistical Manual (DSM), to be published in 2012, certain diagnostic criteria are bizarre and diagnostic thresholds for some illnesses have been lowered (Rev Prescrire n°323). In 2010, the indications for sertraline were extended to cover various anxiety disorders (panic disorder, social anxiety disorder, post-traumatic stress disorder) (Rev Prescrire n°316).

Companies are trying to get their products authorised for use in earlier stages of the disease concerned. For example, gliatiram is now authorised for suspected recent-onset multiple sclerosis (Prescrire Int n°108). This medicalisation serves companies’ interests by expanding the market for their drugs, at the expense of patient safety and well-being.

Some of the advertisements banned by the French regulator (Afssaps) in 2010 are particularly informative:

• misleading comparison and overstated results for Alimia® (pemetrexed) and Loramyc® (miconazole) (Rev Prescrire n°318);
• minimisation of the risks of Botox® (botulinum toxin A) (Rev Prescrire n°318);
• overstated claims concerning the indications for Calciprat vitamine D3° and Caltrate vitamine D3° (calcium + vitamin D3), Gardasil® (papillomavirus vaccine 6, 11, 16, 18), Lacteo® (Lactobacillus acidophilus) and Solacyn® (vitamin A + L cystine + sulphur + yeast) (Rev Prescrire n°318; 323; 326);
• misleading information on the indications for Inoler® (ferrous succinate) (Rev Prescrire n°318);
• unfounded criticism of generic versions of Omexel® (tamsulosin) (Rev Prescrire n°318);
• overly positive presentation of Exforge® (amlodipine + valsartan) and Targen® (valsartan) by opinion leaders (Rev Prescrire n°323).

In the United States, legal action taken against the company marking quetiapine (Seroquel®) revealed the extent to which some firms are willing to go to promote their products: off-label promotion, financial incentives for physicians to write or even simply sign articles on off-label uses. The company was forced to refund public health insurers for the costs of unwarranted prescriptions (Prescrire Int n°112).

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