

Translated from *Rev Prescrire* March 2016; 36 (389): 218-224

Drug packaging in 2015: risky industry choices and lax regulation



Abstract

- *Prescrire* examined the packaging quality of 240 drugs in 2015. No new advances were identified, but drug packaging continues to expose patients to a variety of dangers.
- Some past advances persist: for example, INNs are often more legible, and recent patient leaflets tend to be clearer and more informative. But these measures are not applied to all drugs, and are rarely applied retroactively to older drugs.
- The overall picture in 2015 is that many drugs are difficult to identify, risky or downright dangerous to prepare, or supplied with patient leaflets that fail to correctly inform patients about their medication. And measures to prevent drug poisoning in children need to be completely rethought.
- It is high time for regulators and policy makers to take the issue of drug packaging seriously, so blatant are the signs of their failure to do so: the increasing use of bulk bottles for new drugs; failure to implement guidelines on safe drug packaging (unit-

dose presentations, appropriate dosing devices, etc.); and expanding umbrella brands which, given the dangers they pose to patients, should be banned instead.

- All things considered, healthcare professionals and patients must remain vigilant and report any dangers they identify. A major European initiative on drug packaging is becoming increasingly necessary.

Rev Prescrire 2016; 36 (389): 218-224.

In 2015, *Prescrire* examined the packaging of about 240 drugs available on the French market, some for new drugs and some for older drugs.

Ease of use is an important aspect of a drug's harm-benefit balance. Well-designed packaging contributes to medication safety, while poor design can cause dangerous errors. In some cases, superior packaging will be an element in the choice of treatment. Over the years, *Prescrire's* systematic analyses of drug packaging have identified a number of advances, but also many flaws that could cause or have caused dangerous errors (1-4). This review outlines our findings in 2015.

INN legibility: much progress still needed

During drug treatment, the very minimum requirement for avoiding errors is the ability to clearly identify the active substance or substances the product contains by their international nonproprietary name (INN). The labelling on the packaging (boxes, blister packs, bottles, syringes, etc.) is supposed to help healthcare professionals and patients identify the composition of the drug.

Helping patients recognise their medications. Various measures can emphasise the INN in a highly legible fashion. The absence of an invented name frees up space that can be used to increase the prominence of the INN. For example, pharmaceutical products whose brand name includes the INN as the first term are often associated in practice with labelling that makes the INNs more legible. This is the case for many generics and a few other drugs (Kétoconazole HRA°, Noradrénaline Renaudin°). And the use of bold characters or clear contrast with the background makes INNs easier to identify, as seen with *ponatinib* (Iclusig°). ►►

► From this perspective, wallet-style blister packs, in which the box and blister pack are fused into one, are useful because they provide space to prominently display important information, such as the INN close to the dosage units, as with *enzalutamide* (Xtandi[®]), for example.

But as in previous years, our examination of drug packaging also revealed many examples of labelling in which the INN was overshadowed by the brand name. For example, clear information about the neuropsychiatric adverse effects of the *metronidazole*-containing drugs (Flagyl[®]) has been added to the French patient leaflets. But the INNs are as inconspicuous as ever on the labelling, and particularly difficult to read on the blister packs of tablets.

Umbrella brands: endless confusion. In 2015, umbrella brands were the worst offenders when it comes to making INNs difficult to identify.

An umbrella brand is a range of products (drugs, medical devices, etc.), sold under the same highly visible brand name, that contain different active ingredients, have different benefits and different degrees of harms. The purpose, primarily commercial, is to increase awareness of the brand name (Actifed[®], Doli[®], Fervex[®], Humex[®], Vicks[®], etc.).

In 2015, a new product (Doli État gripal[®]) containing *paracetamol* and *pheniramine* was added to the Doli[®] brand. But the prominently displayed brand name Doli[®] is used for other products containing other active ingredients such as *pseudoephedrine*, a vasoconstrictor with cardiovascular harms that should be avoided, particularly during pregnancy. Patients who confuse two products under the same umbrella brand would be exposed to the risks of the substances contained in the product bought in error, without really knowing what they were ingesting.

Another risk of failure to clearly identify active ingredients on drug labelling is that patients will be exposed to a risk of overdose through the concomitant use of a drug from an umbrella brand and a different product containing the same active ingredient.

Preparing the correct dose of a drug: so many pitfalls to avoid with some notable exceptions!

A suitable pharmaceutical formulation (tablets, multidose oral liquid, injectable solution, etc.) and appropri-

ate packaging must enable users to correctly prepare the dose of the drug to be administered.

In 2015, one example showed that this is attainable, even for an oral liquid form intended for infants: a flavoured oral solution containing *propranolol* (Hemangiolo[®]) was approved for the treatment of severe haemangioma, with a suitable dosing device, a syringe graduated in milligrams.

It is possible to safely package individual doses of dry dosage forms adapted to the varied settings in which drugs are used (in hospital, at home, at school or while travelling). In single-unit presentations, each dose of the drug is protected individually by its immediate packaging, and the label provides all the information required for its safe use: INN, dose strength, formulation, brand name, expiry date and batch number. The unit-dose blisters of *dabigatran* (Pradaxa[®]) or *bromocriptine* (Parlodel Inhibition de la lactation[®]) satisfy this standard.

Bulk bottles instead of blister packs: worsening situation. In 2015, as in previous years, we found that a disturbing number of new drugs are supplied in bulk bottles, even dangerous drugs. Examples include: the cancer drugs *idelalisib* (Zydeligo[®]), *ponatinib* (Iclusig[®]) and *regorafenib* (Stivarga[®]); antivirals such as *ribavirin* (Ribavox[®]), the fixed-dose combinations *ledipasvir + sofosbuvir* (Harvoni[®]) and *dolutegravir + abacavir + lamivudine* (Triumeq[®]); and the antiepileptic *stiripentol* (Diacomit[®]).

Over the years, bulk bottles have become increasingly common compared with blister packs, despite the various advantages of blisters: better shelf-life and the possibility of complete labelling of each dose. This is a bad sign for medication safety on the part of the European Medicines Agency (EMA), which authorises these bulk bottles while also regularly publishing documents about its strategy to prevent medication errors (a)(5).

Complex dose preparation: also with tablets in some cases. Dose preparation is sometimes complex for injectable drugs, if they require several steps for reconstitution or dilution, as is the case with *defibrotide* (Defitelio[®]), *elosulfase alfa* (Vimizim[®]), and *siltuximab* (Sylvant[®]).

In 2015, the antineoplastic *cabozantinib* (Cometriq[®]) was approved for use at one of the following 3 daily doses: 60 mg, 100 mg or 140 mg. But the company produces only two dose strengths, 20 mg or 80 mg hard cap-

sules that it combined in an unusual manner in wallet-type blister packs. Each blister pack has rows of 2 or 4 hard capsules of one or the other of the two dose strengths. The sum of the strengths per row corresponds to the daily dose. The boxes show two values, that of the doses of the hard capsules (20 mg or 80 mg) and that of the daily dose to administer (60 mg, 100 mg or 140 mg). Ultimately, the packaging of *cabozantinib* is so complex that dose preparation requires the prevention of potential dosing errors through explanations, monitoring, and ongoing support.

New dosing frequencies: labelling should include warnings. Unusual or new dosing frequencies can lead to underdosing or overdose. Such errors have occurred with *methotrexate* for example, when weekly tablets were taken daily by mistake (6).

Hydrocortisone sustained-release tablets (Plenadren[®]) for once-daily administration have been authorised in the European Union, whereas this drug has long been available as conventional-release tablets to be taken 2 or 3 times daily. The packaging the drug company sent us does not mention this new dosing frequency.

In 2015, three new dose strengths of *pasireotide* (Signifor[®]) were introduced onto the market, including a 60 mg strength product for monthly intramuscular injection for the treatment of acromegaly. This drug was already available in three dose strengths, including 0.6 mg for daily subcutaneous injection to treat Cushing's disease. While some features enable users to differentiate between these two series of dose strengths, there is no specific statement on the labelling (boxes and blister trays) about their different dosing frequencies. Confusion between the 0.6 mg and 60 mg dose strengths could lead to a 100-fold overdose.

In contrast, other pharmaceutical companies have chosen to inform users more effectively: the dosing frequency (once daily) of *tacrolimus* sustained-release tablets (Envarsus[®]) is stated on the box, which helps differentiate them from *tacrolimus* conventional-release hard capsules for twice daily administration.

a- In late 2015, the EMA published a good practice guide on risk minimisation measures to prevent medication errors, including guidance on drug packaging (ref 5).

How to treat a child when no suitable product is available?

Another type of difficulty with dose preparation is the unsuitability of drugs for paediatric use. For example, the European summary of product characteristics (SPC) for the antiepileptic *stiripentol* (Diacomit[®]) specifies the recommended doses (in milligrams per kilo of body weight), but neither the formulations (fixed-dose hard capsules and sachets of powder) nor the packaging are adapted accordingly. An array of doses to prepare based on the child's weight are listed, but only 2 dose strengths – 250 mg and 500 mg – are provided, without any procedure or dosing device for preparing intermediate doses. Should the powder be divided into smaller doses in hospital? Or does the risk of generating dosing errors fall to the parents?

Similarly, the marketing authorisation for *everolimus* (Votubia[®]) was extended to include the treatment of infants aged 1 year and older. But only fixed dose strengths are available, while the dose to prepare depends on the child's body surface area and the measured *everolimus* whole blood trough concentration. Furthermore, the EU SPC and patient leaflet suggest dispersing the tablet in water inside a graduated syringe, a process that would require manipulation of this cytotoxic drug. Normally graduated syringes are used to administer only a fraction of the suspension obtained. This option could be useful for dose adjustment but is not mentioned in the SPC.

Another common danger with oral liquid formulations is the calculation required to convert the recommended dose in milligrams of drug to the volume in millilitres to be measured, when a dosing device is provided in the box that is graduated in millilitres rather than milligrams. These conversion calculations are potential sources of error (7).

For example, in 2015, *mercaptapurine* oral suspension (Xaluprine[®]) is more convenient for children than the existing tablets, but it is a shame that the syringe is graduated in millilitres of *mercaptapurine* rather than milligrams.

New concentrations of insulins: caution. The insulin market just gets more and more complicated: various mixtures of insulins, various insulin analogues, and various types of pens. To add to the confusion, an *insulin lispro* pen (Humalog[®]) that contains a new strength of 200 units/ml arrived on the market in 2015, while the other insulin pens in France contained

100 units per ml. Risk minimisation measures were planned, but do not eliminate the risk. For patients switching from *insulin* 100 units per ml to *insulin* 200 units per ml, it is important to explain that each unit-dose graduation on the pens delivers the same quantity of drug despite this change, and that they should not halve the number of units. In 2016, the market seems likely to become even more complicated, with the introduction of *insulin glargine* 300 units per ml (Toujeo[®]).

Patient leaflets: new dangers to explain

In the last ten years or so, the quality of patient leaflets for drugs approved through European marketing authorisation procedures seems to increasingly benefit from readability testing by patient groups. They have become clearer and much more informative. Some are outstanding, such as the patient leaflet for *propranolol* (Hemangirol[®]).

Another example: the marketing authorisations for products containing *metronidazole* (Flagyl[®]) have been amended, with the addition of information about psychiatric adverse effects. This information has also been included in the patient leaflet in a way that makes it easy for patients to understand.

This example shows that the patient leaflets of older drugs can and should be updated to comply with current standards. But this rarely occurs: often, when new adverse effects are discovered, they are added to the patient leaflet using terms that patients will not necessarily understand, with no explanation or, worse yet, the patient leaflet is not updated at all. Two examples are presented below.

Vaginal oestrogens, long-term risks. During a review of treatments for vaginal dryness associated with the menopause, we examined the packaging of drugs containing oestrogens alone (*estriol* and *promestriene*) for vaginal use. We found that the patient leaflets contained little information about the risks of these oestrogens, yet they are absorbed systemically through the vaginal mucosa. There was no mention of the risk of thrombosis, breast cancer and endometrial cancer (8). Stating that they are contraindicated for women at risk of venous thromboembolism does not constitute sufficient warning of this risk.

These patient leaflets that failed to inform patients of the risks of oestrogens resulted from old national marketing authorisations from the 1980s and 1990s (Colpotrophine[®], Gydrelle[®], Physiogine[®], Trophicrème[®]). In contrast, the patient leaflet for an *estriol* product (Blissel[®]), approved in 2010, is more informative. The adverse effects section mentions: "certain types of tumours such as endometrial cancer or breast cancer; blood clots in the veins; heart attack and stroke" (9). This example shows that it is possible to do better, provided someone thinks to amend the information provided in obsolete patient leaflets.

Esidrex[®]: an error corrected, but after a delay. In March 2015, following reports from a participant in our practice improvement programme, *Prescrire* informed the French Health Products Agency (ANSM) of an error in the patient leaflet for *hydrochlorothiazide* (Esidrex[®]), a potassium-depleting diuretic (10,11). The company that markets Esidrex[®] had also asked for the patient leaflet to be corrected several years earlier: in the contraindications section, the patient leaflet advised against the use of *hydrochlorothiazide* by patients with hyperkalaemia, which erroneously seemed to suggest that *hydrochlorothiazide* is a potassium-sparing diuretic.

The patient leaflet and the SPC were amended on 18 January 2016 and published online on the ANSM website on 29 January.

Risk of massive ingestion by children: better means of prevention required

Each year, *Prescrire* finds that products containing dangerous or toxic doses are packaged with no child-proof system, even though they are intended to be stored in households in which children could access them unnoticed by their carers. Thus, in 2015, we found that the bottles of the psychoactive agents *hydroxyzine* (Atarax[®]) and *temazepam* 20 mg (Normison[®]) and of *stiripentol* (Diacomit[®]) lack child-proof caps. This packaging should not have been authorised.

Child-proofing drugs, not just bottles. As in previous years, unit-dose blister packs containing tablets or capsules that are sealed with a child-resistant film were rare. Among the 240 drugs we examined in 2015, none of the oral medications were packaged in this way. Yet not only are unit- ▶▶

► dose blister packs a benchmark packaging solution for quality care, but the technical means of child-proofing them have been available for some time (3).

In 2014, *Prescrire* granted a Packaging Award to the first tube we examined that had a child-proof cap: *brimonidine* cutaneous gel (Mirvaso[®]). Serious cases of ingestion by children had occurred during its clinical development. In 2015, another company placed *brimonidine* + *brinzolamide* eye drops on the market (Simbrinza[®]). The patient leaflet for these eye drops mentioned the risk of toxicity if a child were to ingest it, but the company and drug regulatory agencies did not go as far as adding a child-proof system (12).

Making packaging attractive to children increases the risk of accidental ingestion. For example, the *paracetamol* + *pheniramine* combination (Doli État grippal[®]) is a fruit-flavoured, pleasantly tart powder that tastes like candy. It contains doses of *paracetamol* that would be hepatotoxic for a young child. The box is easily opened and the sachets can be torn open by hand. Yet procedures exist to make boxes child-proof and manufacture sachets that can only be opened with a tool.

Regulators' low standards = a cause of poor-quality and dangerous packaging

Drug companies' marketing objectives or efforts to minimise manufacturing costs often undermine the quality of drug packaging. For packaging in the EU, pharmaceutical companies apply the regulatory requirements of title V, "Labelling and package leaflet", of the European Directive on medicinal products for human use (2001/83/EC) (2). These provisions are useful but too imprecise to ensure high-quality packaging. In practice, after examining the packaging of thousands of drugs, it is clear that pharmaceutical companies have considerable room to manoeuvre, which determines the quality or dangers of drug packaging. Bulk bottles or blister packs? Unit-dose or multidose immediate packaging? Accuracy and quality of the dosing device? A syringe graduated in milligrams of the drug or millilitres of solution? Should the brand name or the INN be most prominent? What level of childproofing is needed to prevent a child from ingesting a toxic quantity of the drug? The answers to all these questions are left above all to the pharmaceutical company.

Patient leaflet for Harvoni[®] (sofosbuvir + ledipasvir): almost no information on adverse effects

When we examined the packaging of Harvoni[®] (*ledipasvir* + *sofosbuvir*, a fixed-dose combination of two antiviral drugs with activity against hepatitis C), we were struck by the paucity of information about adverse effects in the patient leaflet. From the first version to the most recent one dated December 2015, the Harvoni[®] patient leaflet astonishingly mentions only two adverse effects: "fatigue" and "headache" (1).

Uncertainty over the adverse effects of sofosbuvir. *Sofosbuvir* monotherapy was approved in January 2014 under the brand name Sovaldi[®]. In our initial evaluation of this drug, we highlighted that the main clinical trial data available about adverse effects were difficult to interpret, due to inadequate evaluation (2). The European patient leaflet for Sovaldi[®] mentions the adverse effects of treatment with the combination of *sofosbuvir* and *ribavirin*, with or without *peginterferon*, but not for *sofosbuvir* alone (3).

However, animal data from rats and dogs that received high doses of *sofosbuvir* show potential haematological, hepatic, gastrointestinal and cardiac toxicity (1). The European Medicines Agency (EMA) is aware of these findings, but they are not mentioned in the European patient leaflet for Sovaldi[®] (2). The patient leaflet features the inverted black triangle symbol indicating, as for any new drug, that limited knowledge has been acquired on their adverse effects (2). But this warning sign is not generally expanded upon by additional information about the specific suspected harms that healthcare professionals and patients should look out for. Yet it is not a rare occurrence that drugs' suspected harms materialise and are subsequently mentioned in the adverse effects section.

In addition, the US prescribing information for Sovaldi[®] also encourages monitoring of *sofosbuvir*'s pancreatic toxicity due to the lipase elevation in certain patients (4).

Are agencies too flexible or do their priorities lie elsewhere? Drug regulatory agencies are generally not very demanding when it comes to the scientific quality of marketing authorisation applications. This is also true when it comes to packaging. Yet they have a role to play in ensuring that implementation of Directive 2001/83/EC meets the highest standards, by drawing up recommendations that protect patients (2).

Patient leaflet for sofosbuvir + ledipasvir: adverse effects that have gone unmentioned. This information has not been mentioned either in the patient leaflet for the *sofosbuvir* + *ledipasvir* fixed-dose combination, which simply warns of cases of fatigue and headache (1).

Yet the clinical evaluation data includes a randomised comparative trial ("Sirius") that provides evidence of several adverse effects of the *sofosbuvir* + *ledipasvir* combination (5). A variety of other disturbing adverse effects were reported in this trial: sleep disorders, pancreatic disorders, hypertension, cough and dyspnoea. Cases of elevation of creatine kinase activity raise the possibility of muscular harms. Preclinical data showed accumulation of *ledipasvir* in the uvea, with pigmented iris (5).

Patient leaflets must protect patients. Patient leaflets make a particularly important contribution to patient safety. The patient leaflet for the *sofosbuvir* + *ledipasvir* combination does not fulfil this function, and the EMA was too lax in its failure to demand that it contain information to protect patients and provide guidance about the kinds of adverse effects they should be looking out for. The Harvoni[®] patient leaflet, as it currently stands, should never have been authorised.

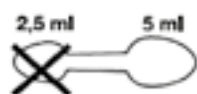
©Prescrire

Selected references from Prescrire's literature search.

- 1- European Commission "Chronological list of variations up to 7 January 2016 + patient leaflets from 17 November 2014 and 18 December 2015 Harvoni": 15 pages.
- 2- Prescrire Editorial Staff "Sofosbuvir. Active against hepatitis C virus, but evaluation is incomplete" *Prescrire Int* 2015; **24** (156): 5-10.
- 3- European Commission "Chronological list of variations up to 7 January 2016 + patient leaflets from 16 January 2014 and 27 May 2015-Sovaldi": 14 pages.
- 4- US FDA "Prescribing information-Sovaldi" 6 December 2013: 30 pages.
- 5- Prescrire Editorial Staff "Ledipasvir + sofosbuvir. A therapeutic advance in genotype 1 hepatitis C virus infection, despite uncertainties" *Prescrire Int* 2015; **24** (166): 285-289.

When recommendations exist, agencies do not necessarily insist on their application. For example, the European Commission's 2009 guidelines on labelling recommend that INNs should be given equal prominence to brand names. These guidelines are very rarely applied, except for generic drugs. And the ANSM has still not published specifications for unit-dose presentations announced in 2008, or its recommendations on dosing devices launched in 2012.

In 2015, a particularly shocking example illustrates how little attention regulators pay to the technical aspects of drugs. In France, the company that markets the *aciclovir* oral suspension 200 mg/5 ml (Zovirax^o) had to change the type of dosing device supplied in the box. It chose a new device, a double-ended spoon, one end for measuring 5 ml and the other 2.5 ml, which is not suitable for the doses recommended in the SPC (5 ml and 10 ml). Rather than supplying an appropriate dosing device, the company and the ANSM mentioned in the SPC and the patient leaflet that the double-ended spoon is unsuitable, which was illustrated by the diagram below (13).



As of early 2016, drug regulatory agencies do not sufficiently anticipate the risks associated with inappropriate packaging, and demand few additional studies that would motivate pharmaceutical companies to improve their development. They do not appear to systematically examine drug packaging. Which dose strengths? Is there a need for fixed dose strength tablets or a multidosed oral liquid form to enable dose adjustment? What type of dosing device should be provided? What type of information should be provided in patient leaflets apart from readability testing?

The case of the patient leaflet for *ledipasvir + sofosbuvir* (Harvoni^o) raises many such questions (see p. 162).

True verification of the packaging mock-ups before marketing authorisation is granted would prevent gross aberrations. For example, in 2014, *dextromethorphan* sachets (Surbronc^o) received a *Prescrire* Packaging Red Card on account of the illustration of someone downing a drink in one go, with the caption "lemon punch flavour", a message that trivialises the dangers of this opioid antitussive that is sometimes misused as a recreational drug. In 2015, the company removed the statement about its flavour (14).

Few resources allocated to improving old packaging. Requests for major variations to marketing authorisations, or even European or national reviews, present an ideal opportunity to improve the packaging of the drugs concerned, but improvements are rare or only minor. For example, despite a major variation for *metronidazole* (Flagyl^o), this drug is still not available in a unit-dose presentation with the INN prominently displayed,

nor is an oral delivery syringe supplied with the oral suspension form. The capacity of the box of *etifoxine* (Stresam^o) has not been reduced despite an ANSM review. A review of benzodiazepines by the French National Authority for Health (HAS) could have prompted an overhaul of their packaging, including the introduction of child-proof unit-dose blister packs containing just a few doses, for occasional insomnia.

The patient leaflets of old marketing authorisations that have become obsolete could be improved when new products containing the same active ingredient are authorised, and for which the patient leaflet contains up-to-date data on harms. For example, if the level of information provided in the patient leaflet for *estriol* vaginal gel (Blissel^o) was imposed on drug companies holding old marketing authorisations for vaginal *estriol*, women would be better informed.

Healthcare professionals and patients: examine packaging, and report flaws more readily

Healthcare professionals can take action to prevent errors: by critically examining packaging, acquiring the "packaging reflex" when choosing which product to prescribe and analysing an adverse effect, sending accurate reports to their national drug regulatory agencies (the ANSM's "Guichet des Erreurs Médicamenteuses" in France) or their local pharmacovigilance centres of any errors or potential dangers even if no error occurred. Examples include: resemblance between different products from the same range, ambiguous statements as to dose strength on labels, inappropriate dosing devices, complex dose preparation methods, risks that could occur if the drug is separated from its packaging, or any information missing from the patient leaflet.


Given the magnitude of the problem, when will a major European initiative on drug packaging be launched, so that regulators, policy makers and the pharmaceutical industry embark on a strategic plan to improve medication safety?

Review produced collectively by the Editorial Staff: no conflicts of interest
©Prescrire

Selected references from Prescrire's literature search.

1- Prescrire Rédaction "Praticité des médicaments: des progrès souvent discrets" *Rev Prescrire* 2015; **35** (382): 577-579.

- 2- Prescrire Rédaction "Praticité et conditionnement: des progrès tangibles" *Rev Prescrire* 2015; **35** (382): 624-629.
- 3- Prescrire Editorial Staff "Drug packaging in 2014. Authorities should direct more efforts towards medication safety" *Prescrire Int* 2015; **24** (160): 136-138.
- 4- Prescrire Editorial Staff "Drug packaging. A key factor to be taken into account when choosing a treatment" *Prescrire Int* 2011; **20** (120): 247-249.
- 5- EMA "Good practice guide on risk minimisation and prevention of medication errors" 18 November 2015: 41 pages.
- 6- Prescrire Editorial Staff "Fatal methotrexate overdose" *Prescrire Int* 2013; **22** (138): 126.
- 7- Prescrire Rédaction "Oxcarbazépine: erreurs de doses" *Rev Prescrire* 2007; **27** (280): 108.
- 8- ANSM "Notices-Colpotrophine" 3 April 2015 + "Notice-Gydrelle" 17 July 2013 + "Notices-Physiogine" 16 May 2014 + "Notice-Trophicrème" 18 September 2015: 28 pages.
- 9- ANSM "Notice-Blissel" 27 September 2012: 8 pages.
- 10- ANSM "Notice-Esisdrex" 8 November 2011: 5 pages.
- 11- Prescrire Rédaction "Notice Esisdrex^o (hydrochlorothiazide)" Letter to the ANSM, 18 March 2015 + ANSM email to Prescrire 2 April + 6 July 2015: 3 pages.
- 12- ANSM "Notice-Simbrinza" 29 May 2015: 9 pages.
- 13- ANSM "Notice-Zovirax" 24 June 2015: 6 pages.
- 14- Boehringer Ingelheim "Surbronc toux sèche" Letter to Prescrire 19 November 2015: 1 page.



Coming soon...

NEW PRODUCTS

- *Febuxostat* and tumour lysis syndrome
- *Adalimumab* and plaque psoriasis in children
- *Nintedanib* and idiopathic pulmonary fibrosis

ADVERSE EFFECTS

- *Zidovudine*, *tenofovir* or *abacavir*? Different adverse effect profiles
- *Nicorandil*: so much needless suffering

REVIEWS

- Progestogens and prevention of preterm birth in women at risk

Outlook

- Electronic prescribing: the risk of errors and adverse effects
- Student action reduces industry influence in US medical schools