

2012 drug packaging review: many dangerous, reportable flaws



Abstract

● Drug packaging plays an important role in protecting and providing information to patients. The packaging examined by *Prescrire* in 2012, on the whole, still fails to perform all of these functions effectively.

● Two issues are especially worrisome. First, packaging too often poses a danger to children. In addition, too many patient leaflets provide incomplete information about adverse effects, thus failing to properly protect the most vulnerable patients.

● Yet, the method *Prescrire* used to analyse drug packaging shows that it is not difficult to detect and anticipate risks. It is up to healthcare professionals to take advantage of the method, to protect patients from, and report, dangerous packaging.

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Drug packaging plays an important role in drug safety and in informing patients about their treatment. Poorly designed packaging can cause confusion about the drug's identity, lead to dosing errors, and expose patients to preventable adverse effects (1,2).

In 2012, as in previous years, *Prescrire's* Packaging Working Group thoroughly analysed the packaging quality of the drugs evaluated during the year in our French edition. The situation in 2012 is similar to previous years: drug packaging is important but receives too little attention.

In 2012, children appear to be the population group most overlooked in the marketing authorisation process, in terms of packaging (2).



Think about children first

Are drug regulatory agencies and pharmaceutical companies concerned about children accidentally or erroneously exposed to drugs intended for adults? The situation is common, since medicines are present in almost every household.

Various examples identified in 2012 illustrate the extent of the problem.

No child-proof cap: poisonings, accidents. The risk of accidental ingestion of caustic household products, such as hydrochloric acid or sodium hydroxide, by children is well known (3). But the need to protect children from drug toxicity seems to have escaped the attention of health authorities, given the quantity of drug bottles on the market that lack a child-proof cap (1,2).

Some examples of bottles without a child-proof cap in 2012: *Preterval*^o (*perindopril + indapamide*), *Predyl*^o (*povidone-iodine*), and *Codotussyl toux sèche*^o (*pentoxiverine*).

Paracetamol overdose provokes serious or even fatal hepatic disorders. A retrospective study has shown that the orodispersible form of *paracetamol* tablets in particular exposes children to a risk of overdose (*Prescrire Int* n^o 132). Yet in 2012, bulk tubes

containing a total of 8 g of orodispersible *paracetamol* were available for self-medication in France without a child-proof cap (*Effergalnodis*^o). These pleasantly tart, fruit-flavoured, effervescent tablets resemble mint candies. This product represents a danger to children and should be withdrawn from pharmacies.

Improvement is possible, however: *Paratabs*^o contains 6 g of orodispersible *paracetamol* in child-resistant blister packs (a).

Blister packs that are too easily opened. Other dangerous drugs are marketed in blister packs covered with a film that is easily peeled off, such as *Suboxone*^o sublingual tablets containing 2 mg or 8 mg of the opioid *buprenorphine* combined with *naloxone* (*Rev Prescrire* n^o 342). And the tablets give off a lemon aroma when they are removed from the blister pack.

Beware of alcohol. The use of alcohol-based hand sanitisers is now widespread. Accidental ingestion of these products by children has resulted in acute poisoning, with inebriation, agitation, drowsiness and impaired consciousness (*Prescrire Int* n^o 129). Although they are not drugs, cases of this type show that more thought must be given to the risks to which children are exposed due to the presence of alcohol and to excipients used in drug formulations.



Children are particularly vulnerable to errors.

In 2012, French poison control centres published a study that identified, over a 2-month period, 169 reports of administration errors involving single-dose containers: 79% of the victims were children under 5 years of age. In 151 cases, the confusion was linked to the packaging. Two children suffered serious adverse effects (*Rev Prescrire* n° 345).

The consequences of accidental injection of *adrenaline* via autoinjectors have sometimes been serious, including finger amputation and death (*Prescrire Int* n° 131). Several reports concerned children.

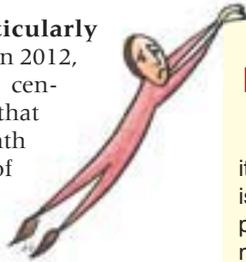
The recommended dosage for Flixivate° (*fluticasone* cream and ointment) is one cutaneous application per day (*Rev Prescrire* n° 341). Yet the dosing schedule on the packaging shows 2 boxes, labelled "morning" and "evening", implying that it should be applied twice daily, thus exposing infants aged between 3 months and 1 year to the adverse effects of an overdose of a high-potency topical corticosteroid.

European Paediatric Regulation: mainly benefiting the drug industry.

In 2012, five years after the European Paediatric Regulation came into effect, the European Commission opened a public debate on its impact (b), giving *Prescrire* the opportunity to share its conclusions that the results have been disappointing. This Regulation benefits pharmaceutical companies, while children have gained little (2,4).

In March 2011, we evaluated Cozaar° (*losartan* oral suspension), an expensive product with dangerous packaging, for which the pharmaceutical company did not request reimbursement (*Rev Prescrire* n° 329). And yet this earned the company, MSD, a 6-month extension for its market monopoly on the drug, including the formulations intended for adults.

Another notable example in 2012: the European marketing authorisation (MA) for Revatio° (*sildenafil*) was extended in May 2011 to include children aged 1 year or older with pulmonary arterial hypertension (*Prescrire Int* n° 129). In France, however, the paediatric form was not marketed until 17 months later (5). In the meantime, pharmacists had to prepare oral suspensions from tablets for adults using a 14-step procedure, or from the powder form of the drug, and then package these suspensions in bottles. This tricky preparation process added a risk of dosing errors for a drug that can be fatal to children (6).



Prescrire's packaging analysis

A drug's packaging refers to all of the items that either protect it until its administration or provide information useful for patient care: the drug's name (INN), information on dosing, drug interactions, adverse effects, preparation and administration, storage (1). It must help to prevent medication errors and accidental ingestion by children. Packaging is therefore an important component of a drug's harm-benefit balance.

Over 5000 analyses in 30 years.

Prescrire analyses the packaging of the new drugs evaluated in the "New Products" section of its French edition, *la revue Prescrire*.

It also re-examines the packaging of existing products when changes are introduced: name change, different dosing device, usage broadened to include vulnerable patients (children, pregnant women, patients with renal impairment), major new data on adverse effects, etc. *Prescrire's* Packaging Working Group then checks whether any item of the packaging is more dangerous as a result of these changes: is the INN harder to read, the closure too weak or the dosing device dangerous or unsuitable? And is the information about pregnancy ambiguous or has information about adverse effects been omitted?

Prescrire analyses the packaging of about 150 drugs every year, and has examined over 5000 products in the past 30 years.

Systematic analysis. Every item of the packaging is examined in detail using a standardised form. When the drug is part of an umbrella range, we compare its appearance with the other products in the range. We check the labelling for the legibility and position of key information (INN, dose strength, storage, etc.).

We test the quality of blister pack films and bottle caps, especially for dangerous drugs.

We test whether tablets are easily divisible. We prepare formulations that require reconstitution. We try out dosing devices, referring to the patient leaflet. We check whether oral delivery syringes could be attached to an injection needle. We taste and smell the drug. We analyse the usability and safety of the information provided, especially in the patient leaflet, including symbols, pictograms and dosing schedules.

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1- *Prescrire* Editorial Staff "Drug packaging. A key factor to be taken into account when choosing a treatment" *Prescrire Int* 2011; 20 (120): 247-249.

2012: let's remain vigilant to the risks

Too little progress was observed in 2012. Yet examples of suitable packaging are already on the market. This demonstrates that advances are not necessarily adopted in the field of packaging, and that drug companies are neither sufficiently motivated nor required to do better.

Minor improvements. In 2012, only minor advances were made in terms of packaging: the Pegasys° (*peginterferon alfa-2a*) ready-to-use pen with a needle shield that conceals and protects the needle; and the Avonex°Pen° (*interferon beta-1a*) pen as an alternative to pre-filled syringes.

There were improvements in the packaging of some drugs, but they were not sufficient to prevent all of the identified risks. For example, the oral rotavirus vaccine Rotarix° is now ready to use, but the

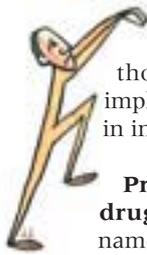


oral applicator still resembles a syringe for injection. It is possible to force a needle onto it and inject the vaccine by mistake.

The *quinine* + crataegus (dry hawthorn extract) combination Okimus°, marketed for the treatment of cramps, is now packaged in blister packs instead of bulk bottles. This improvement does not justify keeping it on the market, given its unfavourable harm-benefit balance.

Child-proof caps have been added to the bottles of Uvestérol° D and Uvestérol° ADEC vitamin solutions, but the announced change to the formulation of these solutions has yet to ►►

a- Child-resistant blister packs are covered with a strong film that is difficult to break without a sharp object. To remove the tablet, the pre-cut blister pocket must first be detached from the strip, freeing an unattached corner of film which can then be lifted in order to peel off the safety film.
b- In 2012, the European Medicines Agency conducted a public consultation on draft guidelines on the development of paediatric drugs, the packaging component of which was grossly inadequate. *Prescrire* participated in this consultation by offering 20 constructive proposals on improving the evaluation, quality and supervision of packaging to make it safer for children, including a major evaluation at the European level of the risks associated with excipients (ref 2).



► materialise. They remain on the market, unchanged, even though they have probably been implicated in life-threatening events in infants.

Prescribe, dispense and refer to drugs by their INN. A drug's real name, its international nonproprietary name (INN), makes it possible to identify the same active ingredient in various products. This is the name that should be emphasised, especially in order to prevent overdoses and manage the risk of drug-drug interactions.

The INN was given due prominence on some of the packaging analysed in 2012: *norgestrol* and *estradiol* were displayed in bold type on the box and blister pack of Zoely[®]; the brand name Bétahistine Bouchara-Recordati[®] includes the INN; and the INN and dose strength are clearly displayed on the single-unit blisters for Pentasa[®] (*mesalazine* 1 g), Pradaxa[®] (*dabigatran* 150 mg), and Zelboraf[®] (*vemurafenib*).

But as in previous years, most packaging examined emphasised the brand name, using large, bold type, while the INNs were displayed in small, light-face type without sufficient background contrast. They are sometimes so stylised as to be barely legible, for example on the box for Aldalix[®] (*spironolactone* + *furosemide*) (c). Again in 2012, some drugs were authorised for sale despite the absence of the INN on packaging items such as the single-dose containers of Saflutan[®] (*tafluprost*) and the blister packs of Gélutrophyl[®] (*thenoic acid*).

Resemblances between dose strengths, umbrella brands: danger!

In 2012, the packaging of too many different dose strengths from the same product line looked so similar that it could be a source of confusion for users: for example, Xeroquel[®] extended-release 300 mg and 400 mg (*quetiapine*), Xarelto[®] 15 mg and 20 mg (*rivaroxaban*), and Sycrest[®] 5 mg and 10 mg (*asenapine*).

Even more troubling, the French health products agency (ANSM) took no steps in 2012 to ban or strongly recommend against the use of umbrella brands. This practice has become widespread in the self-medication sector: different drugs with different indications and adverse effect profiles are sold under similar brand names, in packaging that often looks very similar (for example, under the umbrella brand Advil[®]: RhinAdvil[®] (*ibuprofen* + *pseudoephedrine*) (*Rev Prescrire* n° 345) (7).

Dosing devices: bad habits persist.

In 2012, the oral delivery syringe supplied with Oxynorm[®] 10 mg/ml (*oxycodone* oral solution) combines the major known

flaws of dosing devices: it is graduated in millilitres instead of milligrams, creating a risk of confusion between the two units of measurement; there is no graduation for the 2.5 mg dose indicated in the summary of product characteristics (SPC) for patients with renal impairment; and its capacity is too large for the preparation of low doses (1 mg or 2 mg).



Incomplete patient leaflets: dangerous for patients

More patient leaflets examined this year provided incomplete information about adverse effects (d).

Reports of QT interval prolongation triggering cardiac arrhythmia, including sometimes fatal torsades de pointes, have been attributed to oral *domperidone*. Yet the patient leaflet for Bipéridysflash[®] (*domperidone*), which was introduced in France in October 2011, does not mention the risk of cardiovascular adverse effects or dangerous interactions with other drugs that can prolong the QT interval (*Rev Prescrire* n° 340) (8).

Beware of paracetamol. The patient leaflets for products containing *paracetamol* are inconsistent, particularly the warnings provided about interaction with alcohol. The leaflets for Paratabs[®] are clear (our translation): "if you regularly drink large quantities of alcohol, you may need to take lower doses [of paracetamol] and limit your alcohol intake for a short period of time, otherwise it could damage your liver" and "avoid taking (...) with large quantities of alcohol" (9).

These explanations contrast with those in the patient leaflet for Efferalgantab[®], which simply mentions that the maximum daily dose in case of chronic alcohol abuse is 3 g and advises to (our translation) "take special care (...) in case of alcohol abuse" (10). When will patient leaflets for useful drugs finally be harmonised up to the highest standard?

Important information missing.

The patient leaflet we examined for Mycohydralin[®] cream (*clotrimazole*) intended for vulvar application does not mention whether it can be used with latex condoms (11). However, the patient leaflet for the vaginal tablets (*Rev Prescrire* n° 342) advises against using them with latex condoms due to the risk of condom breakage (11). We contacted the company and were told that an application to improve the patient leaflet for the cream

is planned, with the addition of this information, but it had not yet been submitted as of 30 October 2012.

The European patient leaflet and SPC for Difclir[®] (*fidaxomicin*) make no mention of the risk of serious gastrointestinal haemorrhage (12). Yet the risk is significant and is mentioned in the US prescribing information (13).

Labelling also includes useful information. In 2012, the box for Ostram Vitamine D3[®] (*tricalcium phosphate* + *colecalfiferol*) no longer mentions that the drug is contraindicated in patients with renal impairment, and the word *phosphate* is not printed on the front of the box. This is a regrettable step backwards because healthcare professionals could easily forget that Ostram[®] contains a *calcium phosphate* salt, while equivalent products containing *calcium carbonate* salts are not contraindicated in these patients.

NSAIDs: patient leaflets should clearly deter their use throughout pregnancy.

The patient leaflet for Alevetabs[®] (*naproxen*) states that (our translation) "during the first 5 months of your pregnancy, your doctor may prescribe this medication, if necessary" (14).

Some information provided in the patient leaflets for RhinAdvil[®] and Rhinureflex[®] (*ibuprofen* + *pseudoephedrine*), although not incorrect, is convoluted and ambiguous, and leaves the door open to the use of NSAIDs during pregnancy depending on "the opinion of your doctor or pharmacist" (our translation) (15,16).

Exposure to NSAIDs in early pregnancy carries a documented risk of spontaneous abortion. A risk of fetal malformations cannot be ruled out (*Rev Prescrire* n° 341). There is solid evidence that prenatal exposure to NSAIDs during the second and third trimesters of pregnancy poses a risk of premature closure of the ductus arteriosus, pulmonary arterial hypertension and renal failure. In addition, low-level evidence concerning *pseudoephedrine* is consistent and points to an increased risk of teratogenesis (*Rev Prescrire* n° 248).

NSAIDs should never be used during pregnancy: patient leaflets for NSAIDs that do not state this clearly pose a risk to the unborn child, and the risk increases when the NSAID is combined with *pseudoephedrine*.

In summary. Healthcare professionals can play a role in improving drug packaging by reporting any identified errors, suspected risks and observed flaws: poorly legible INNs, unsuitable dosing devices,

etc. (e). They should choose medicines with the best packaging, advise patients on their use (helping them to identify the INN on labelling, explaining the use of dosing devices), and inform patients about adverse effects that have been omitted from the packaging.

With innovation in new drugs or new indications at a standstill, we could at least expect improvements in the packaging of existing drugs. The pharmaceutical industry and drug regulatory agencies have a duty to embark upon a major packaging safety programme to improve existing packaging, paying particular attention to children and other vulnerable patients. This includes improving the quality of paediatric packaging, banning bottles without a child-proof cap, testing the various models of child-proof caps, requiring child-resistant blister packs for particularly dangerous drugs, improving information about overdose in SPCs and encouraging studies by poison control centres on unintentional poisoning.

It is equally urgent that drug regulatory agencies and especially agency rapporteurs responsible for evaluating marketing authorisation applications should anticipate the inherent risks of the proposed packaging and the risk of medication errors before marketing authorisations are granted.

How many years, accidents and deaths will it take before health authorities recognise the importance of drug packaging and take appropriate action?

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c- The INNs on the Aldalix^o box are tiny, resembling little more than a line drawn underneath the brand name. The boxes for Aldactone^o (spironolactone alone) and Aldactazide^o (spironolactone + altizide) have the same flaw. These boxes all look alike and have similar brand names. The withdrawal of Aldalix^o from the French market is a welcome development.

d- Although not actually dangerous, some information about adverse effects provided in patient leaflets is disconcerting, to say the least. For example, in the European patient leaflet for Victrelis^o (boceprevir), the following adverse effects were classified under "mental illness": memory loss, anger, and trouble concentrating (ref 17).

e- In France, any packaging flaws should be reported to the medication errors office of the French health products agency (ANSM): erreur.medicamenteuse@ansm.sante.fr or fax +33 (0)1 55 87 33 10. They can also be reported to Prescrire's Preventing the Preventable programme: <http://evitable.prescrire.org/fr>.

Selected references from Prescrire's literature search.

- 1- Prescrire Editorial Staff "2011 drug packaging review: too many dangers and too many patients overlooked" *Prescrire Int* 2012; **21** (127): 133-138.
- 2- Prescrire Editorial Staff "Packaging of medicines for paediatric use: Prescrire's constructive proposals" *Prescrire Int* 2012; **21** (131): 249-250.
- 3- Comité de Coordination de Toxicovigilance "Ingestion de substances irritantes ou corrosives: étude descriptive des cas avec atteinte endoscopique enregistrés par les centres antipoison et de toxicovigilance d'avril 2009 à mars 2010" February 2012: 37 pages.
- 4- Prescrire Editorial Staff "Who benefits from the European Paediatric Regulation?" 28 November 2012: 6 pages. english.prescrire.org
- 5- ANSM "Revatio poudre pour suspension buvable" 26 October 2012: 1 page.
- 6- FDA "FDA recommends against use of Revatio in children with pulmonary hypertension" 30 August 2012: 2 pages.
- 7- Prescrire Editorial Staff "Prescrire's response to the public consultation on EMA/275297/2010 "Draft - QRD recommendations on pack design and labelling for centrally authorised non-prescription human medicinal products" 29 June 2011: 5 pages. english.prescrire.org
- 8- ANSM "Notice-Bipérididysflash" 4 August 2011: 5 pages + "Notice boîte" May 2011: 2 pages.

9- ANSM "Notice-Paratabs" 28 October 2010: 7 pages.

10- ANSM "Notice-Efferalgantab" 16 July 2012: 6 pages + "Notice boîte" 15 April 2011: 2 pages.

11- ANSM "Notice-Mycohydralin crème" 23 June 2011: 4 pages + "Notice boîte" February 2011: 2 pages + "Notice boîte-Mycohydralin comprimés vaginaux" February 2011: 2 pages.

12- European Commission "Package leaflet-Dificlor" 29 October 2012: 10 pages + "Particulars on box" March 2012: 2 pages.

13- FDA "Label-Dificid" 27 May 2011: 14 pages.

14- ANSM "Notice-Alevetabs" 10 November 2011: 7 pages.

15- ANSM "Notice-Rhinadvil Rhume" 6 August 2012: 9 pages + "Notice boîte-Rhinadvil" 17 June 2008: 4 pages.

16- ANSM "Notice-Rhinureflex" 18 December 2006: 2 pages.

17- European Commission "Package leaflet-Victrelis" 31 July 2012: 13 pages.

english.prescrire.org

Medicines in Europe

See also Prescrire's response to an EMA consultation on potential medication errors: "Safety and usability of packaging and labelling: assessment is required prior to marketing authorisation for all medicinal products, not just for copies of existing drugs (November 2012)".

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