

Abstract

- **Problem packaging is a major concern for patients who are more vulnerable to adverse effects, particularly children and pregnant women. Several problems were noted with products intended for self-medication (umbrella brands), oral solutions sold with dosing devices, and injectable drugs.**

● Looking back at 20 years of Red Cards that *Prescrire* has issued to products with dangerous packaging reveals several improvements, but too many dangers persist.

● **Urgent action needs to be taken by regulatory agencies and drug companies: patient leaflets must be more explicit with regard to adverse effects, especially those of nonsteroidal anti-inflammatory drugs during pregnancy; accidental ingestion by children must be prevented; and companies must design safer dosing devices. Healthcare professionals and patients must remain vigilant and report all packaging issues to the relevant authorities.**

Rev Prescrire 2014; 34 (364): 144-148.



In 2013 as in previous years, the *Prescrire* Packaging Working Group carried out its annual assessment of the packaging quality for most of the drugs examined in our French edition. About a dozen of the 250 product packaging we examined were found to help patients or promote quality of care. Some were improved versions of existing packaging. Conversely, nearly 40 products were found to have poor-quality or even dangerous packaging (see p. 139).

Signs of improvement

Well-designed drug packaging is rare, but some packaging stands out from the rest in terms of quality.

A clearly identifiable INN. The international nonproprietary name (INN) should be clearly and prominently displayed on the packaging to help prevent serious adverse effects due to confusion between similar products, and overdose due to concomitant use of two products containing the same drug. In 2013, the INN was clearly visible on some drug packaging, separate from the brand name. This was the case for *bortezomib*

(Velcade[®]), *decitabine* (Dacogen[®]), and *benzoyl peroxide* (Papclair[®] 5%).

Key healthcare information on the outer packaging. Information of a non-commercial nature is rarely highlighted on the outer packaging, but some manufacturers stood out in 2013. For example, boxes of *pertuzumab* (Perjeta[®]) clearly mention the need to store the product in a refrigerator. Similarly, the word “cytotoxic” is clearly printed on boxes of *cabazitaxel* (Jevtana[®]) (a). And boxes of the neuroleptic *haloperidol* (Haldol[®] 1 mg and 5 mg) mention product modifications made in late 2012.

Easier to prepare. In 2013, packaging features of three drugs simplified their administration.

BCG-Medac[®] for intravesical instillation in bladder cancer uses a closed system for preparing the suspension, along with appropriate urinary catheters and an adhesive bag for waste disposal. This packaging was cleverly designed to minimise potential risks, including preparation errors, needlestick injury and contamination, and therefore received the Prescrire Packaging Award (see April 2014 issue).

Preparation of *degarelix* (Firmagon[®]) was facilitated and made safer by providing the solvent in a prefilled syringe and by adding a transfer device.

Pouches of *morphine* for injection (*morphine-Renaudin*[®]) simplify dose preparation in some situations, although care must still be taken in selecting the correct dose strength.

Some measures to protect children. Infants are especially sensitive to the systemic effects of potent topical corticosteroids. Boxes of topical *fluticasone* (Flixovate[®]) used to bear two dosing schedules (“morning and evening”) that created a risk of overdose, as only a single daily application is recommended for infants. This flaw earned the company a packaging Red Card in 2012 but was corrected in 2013. This is one of several examples of improvements made following *Prescrire*’s alerts (see inset page 139).

Safety improvements were also made in the packaging for other drugs. In 2013, a tamper-proof film was added to blister packs of *buprenorphine* (alone or combined with *naloxone*; Subutex[®], Suboxone[®]). The film is difficult to pierce or to peel off, thus making it more difficult for children to access the contents. In 2012, unsecured Suboxone[®] blister packs earned the company a Red Card.

The *quinine*-containing combination (Okimus[®]), which earned a Red Card in 2008, is no longer sold in bulk bottles without a tamper-proof cap, but in blister packs; this is a welcome move but does not change the fact that this drug, used to treat cramps, should be avoided.

Bottles of *colecalfiferol* (ZymaD[®]) are more difficult to open, as they are now equipped with a child-proof cap.

Dosing devices: the French authorities react. In 2013, the Medication Errors Working Group of the French Health Products Agency examined the quality of dosing devices for oral solutions and made several recommendations open for public consultation (2,3). *Prescrire* responded by highlighting the value of choosing single-dose forms when appro-

priate, and by setting out a list of principles designed to minimise dangers associated with dosing devices, especially for children (4).

Locating the black triangle on patient leaflets. In 2013, new EU pharmacovigilance rules required some products to carry an inverted black triangle, signifying that the drug is being closely monitored for suspected serious adverse effects.

The black triangle reminds patients of the importance of reporting adverse drug reactions to health authorities (mainly regional pharmacovigilance centres in France), but the accompanying information is inadequate.

Urgent changes needed

The above-mentioned improvements are all conducive to safer care. However, most of the packaging for about 5000 products examined by *Prescrire* over more than 20 years have been of poor quality or even dangerous, for various reasons: failure to grasp the importance of drug packaging in treatment safety; priority given to marketing; and attempts to minimise design and manufacturing costs. Yet many risks could be avoided by implementing simple solutions, particularly since examples of suitable packaging are already on the market.

Visibility of the word “pregnancy” in NSAID patient leaflets: a European review is essential. The risk of miscarriage following exposure to NSAIDs in early pregnancy is well documented, and NSAID exposure during this period may also cause malformations (5). It is well established that NSAID exposure during the 2nd and 3rd trimesters can lead to premature closure of the ductus arteriosus, pulmonary hypertension and renal failure in the fetus.

In the early 2000s, the former European Pharmacovigilance Committee recommended that all NSAID summaries of product characteristics (SPCs) mention the risk of miscarriage, cardiac malformations and gastroschisis in case of exposure during the early stages of pregnancy (6). But the French agency preferred ambiguous wording which implied NSAIDs could be used before the 6th month of pregnancy (7).

To protect women who are already pregnant or who are likely to conceive, all NSAID patient leaflets must contain accurate, unambiguous and up-to-date information on the harms associated with these drugs.

Adverse effects and patient leaflets: it takes more than a symbol to protect patients. The patient leaflet is the main source of information for users. “Readability” tests conducted by target patient groups have led to some improvements. Unfortunately, they fail to prevent the inclusion of some dangerously reassuring statements, such as those found in the European leaflet for the cytotoxic drug *ruxolitinib*: “most of the side effects of *Jakavi*[®] are mild to moderate and will generally disappear after a few days to a few weeks of treatment” (8). This wording minimises the risk of serious bleeding and confusion associated with *ruxolitinib*.

A black triangle (▼) is now used to draw attention to drugs suspected of having serious adverse effects that need to be closely monitored. However, it would be better if these dangers were clearly specified in a separate section of the patient leaflet.

For example, *ceftaroline* (Zinforo[®]) was found to damage the kidneys of experimental animals. In clinical trials, 11 patients developed renal failure during treatment with *ceftaroline*, compared to only 5 patients treated with *ceftriaxone* or *vancomycin*. Two sentences in the Zinforo[®] patient leaflet mention an effect on the kidneys, among other adverse effects, but they fail to explicitly link this risk to the presence of the black triangle: there is no way of knowing that nephrotoxicity is a particular focus of attention for the EMA and the FDA (9).

Similarly, the reasons for special monitoring are not mentioned in the patient leaflets for the following drugs:

- *Denosumab* (Prolia[®]): risk of pancreatitis (10);
- *Glycopyrronium* (Seebri Breezhaler[®]): cardiovascular and cerebrovascular risks (11).

The black triangle is useful but not sufficient. Patients have the right to receive all the information needed to protect them from drug-related harms, including suspected harms for which there is sufficient evidence to warrant further assessment. To benefit patients, and not drug companies, uncertainties about adverse effects must be explained.

Umbrella brands: French agency must impose stricter conditions. In 2013, several product lines for self-medication or OTC medicines were extended or modified in France: -advil-[°]; Clarix-[°]; Doli-[°]; Drill-[°]; Humex-[°]; Micro-lax[°]; -sédermyl[°]; Trophirès[°]; and ►►

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a- Regarding cabazitaxel-Jevtana[®], the European Pharmacovigilance Risk Assessment Committee (PRAC) issued an alert concerning errors made during dilution of the solution (ref 12).

► Vicks°. Each of these umbrella brands includes products containing very different active ingredients, some of which can be hazardous, such as *pseudoephedrine*, *dextromethorphan*, and *paracetamol* (in case of overdose). These differences in composition are a source of confusion, yet the packaging for a given product line uses a similar graphic layout. In addition, the INNs are never clearly legible, or sometimes hidden.

For example, on boxes of two Clarix° products containing *dextromethorphan* that we examined in 2013, the brand name for the product line is accentuated at the expense of the INN, even though the manufacturer declared that the INN was part of the brand name.

On boxes of Trophirès composé enfants°, the word "*paracetamol*" is far less visible than the brand name "Trophirès". Yet it is *paracetamol* that should be highlighted in order to avoid overdose due to concomitant ingestion of other *paracetamol*-containing medications, especially as other paediatric medicines in this product line do not contain *paracetamol*.

Many other examples show that companies which market umbrella brands, and the regulatory agencies which authorise them, fail to take account of the inherent risks of these product lines.

More studies needed to evaluate the risk of accidental ingestion. Each year, a large number of dangerous drugs continue to be sold in bulk bottles. Only some are equipped with a child-proof cap: in 2013, this was the case for *pazopanib* (Votrient°), *lapatinib* (Tyverb°) and *methylphenidate* (Ritalin° LP 10 mg).

Older products examined in 2013 are still not equipped with a child-proof cap, even though the substances they contain can have serious adverse effects in case of overdose: they include *dextromethorphan* + *mepyramine* (Clarix toux sèche dextrométhorphan mépyramine adultes°), *alimemazine* (Theralene° syrup), and *clonazepam* (Rivotril°). Worse yet, the packaging for Bricanyl 5 mg LP (*terbutaline*) has become less safe: previously sold in blister packs, this drug is now packaged in bulk bottles without a child-proof cap, even though the tablets are small enough (5 mm) to be ingested quickly, creating a risk of cardiac events.

In view of the increasing number of products sold in bulk bottles, a thorough assessment of the risks inherent in this type of packaging needs to be undertaken. Parents and healthcare professionals should be aware of the risk of accidental ingestion and should report any related accidents.

Dosing devices: strict rules urgently needed. Given the dangers associated with dose preparation of drugs in liquid form, drug companies and regulatory agencies should promote the use of ready-to-use unit doses. When the use of a dosing device is unavoidable, it must be designed to minimise the risk of errors when preparing unit doses. Unfortunately, the situation worsened in 2013.

In 2013, a new 10% *paracetamol* solution with a concentration about 3 to 4 times higher than usual was marketed in France, adding to the many existing paediatric solutions. Under the same brand name, Dolstic°, the company now markets two products for children in different age groups, containing different dosing devices. These two products have similar labelling. Use of the large dosing device intended for children aged 3 to 10 years to prepare a dose for an infant could result in serious overdose.

In 2013, an oral solution of *sildenafil* (Revatio°) dosed at 10 mg/ml and approved for children with pulmonary arterial hypertension was marketed in particularly complex packaging. In addition to an oral syringe for administration, the boxes contain a cup for measuring the amount of water required to reconstitute the suspension, which must not be confused with the dosing device. The oral syringe, graduated in millilitres, bears superfluous markings that exceed the maximum recommended dose. All of these features contribute to the risk of overdose and compound the dangers of a drug that has more harms than benefits in children and whose life-threatening adverse effects are dose-dependent.

Instead of seizing the opportunity to change the concentration of the solution, the company that sells the antiepileptic drug *lacosamide* (Vimpat°) still provides a poor-quality cup graduated in millilitres, which is not sufficiently precise to prepare the required dose of this antiepileptic drug, even for adults.

The large number of low-quality dosing devices identified during our 2013 review is highly disturbing, as they pose a risk, especially to children. All parties concerned must take note of these dangers and make appropriate changes.

Progress is at hand: why wait?

A number of packaging improvements were introduced in 2013, and some regulatory agency departments started to take packaging issues more seriously. Yet the number of products with unsafe packaging remains too high and continues to increase year after year.

Several examples show that it does not require much effort to design safe and appropriate packaging. This goal is within the scope of all drug companies. So why do health authorities hesitate to impose safe, informative packaging and thereby fulfil their responsibility to protect patients?

Therapeutic innovation may be stagnating, but we could at least expect improvements in packaging design.

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- 1- Prescrire Editorial Staff "2012 drug packaging review: many dangerous, reportable flaws" *Prescrire Int* 2013; **22** (138): 134-137.
- 2- ANSM "Projet: Recommandations relatives aux dispositifs d'administration des spécialités sous forme buvable en multidoses (hors produits homéopathiques)" 31 July 2013; 2 pages.
- 3- ANSM "Groupe de travail erreurs médicales - Compte rendu de la séance du 22 mars 2013" 25 April 2013; 11 pages.
- 4- Prescrire Rédaction "Réponse de Prescrire à l'enquête publique de l'ANSM sur son Projet de Recommandations relatives aux dispositifs d'administration des spécialités sous forme buvable en multidoses" 5 September 2013; 17 pages.
- 5- Prescrire Rédaction "À écarter en cas de grossesse: les anti-inflammatoires non stéroïdiens (AINS)" *Rev Prescrire* 2013; **33** (358): 604-605.
- 6- PhVWP "SPC and PL Wording for Non-Steroidal Anti-inflammatory Drugs (NSAIDs) with regard to disturbances of female fertility as agreed by the PhVWP" May 2004; 3 pages.
- 7- Afsaps "Réponse à Prescrire" 22 February 2012; 2 pages.
- 8- European Commission "Leaflet-Jakavi°" 13 November 2013; 7 pages.
- 9- European Commission "Leaflet-Zinforo°" 23 August 2012; 6 pages.
- 10- European Commission "Leaflet-Prolia° pre-filled" 15 November 2012; 13 pages.
- 11- European Commission "Leaflet-Seebri Breezhale°" 28 September 2012; 12 pages.
- 12- EMA "Pharmacovigilance Risk Assessment Committee (PRAC) minutes of the 7-10 October 2013 meeting. 4.1.3. Cabazitaxel-Jevtana°" 7 November 2013; 18-19.



Prescrire's Red Cards for drug packaging, 1991-2012: some improvements, but many dangers persist

Since 1991, as part of its annual Prescrire Awards, *Prescrire* has issued more than 100 Red Cards for poor-quality packaging. The reasons were varied:

- Dangers, especially for children, due to the lack of a child-proof cap on bulk bottles, easily peeled blister packs, or an attractive flavour or shape;
- Incomplete or misleading information in the labelling or patient leaflet;
- Lack of a suitable dosing device;
- Similar appearance of different products marketed under an umbrella brand, creating a risk of confusion between products with very different compositions;
- Presentations that trivialise a drug or increase the risk of overdose.

In October 2013, we re-examined the packaging of these drugs to see if there had been any improvements (a).

Some products more secure. Some companies have made efforts to prevent accidental exposure of children. This is the case for Sectral[®] oral solution 40 mg/ml (*acebutolol*), whose bottles are now equipped with a child-proof cap (*Rev Prescrire* n° 266), and also Suboxone[®] tablets (*buprenorphine + naloxone*), which have been marketed since 2013 in unit blister packs equipped with a tamper-proof film that restricts access by children (*Rev Prescrire* n° 342; n° 362). The *quinine*-containing combination (Okimus[®]), authorised for cramps, has been sold since late 2012 in blister packs rather than bulk bottles, although it remains a drug to avoid (*Rev Prescrire* n° 297; n° 352).

In contrast, no improvements were made in the packaging of tablets containing *methotrexate* (Imeth[®], Méthotrexate Belion[®], Novatrex[®]) or that of *Quinimax*[®] tablets (*quinidine + quinine + cinchonidine + cinchonine*), which are still sold in bulk bottles without a child-proof cap, even though the bottles contain enough tablets to kill a child (*Rev Prescrire* n° 352; n° 231).

Vials of Dolko[®] oral *paracetamol* solution, as well as Toplexil[®] syrup (*oxememazine*) and Zarontin[®] (*ethosuximide*, an antiepileptic drug) are still not equipped with a child-proof cap (*Rev Prescrire* n° 284; n° 309; n° 359).

Some improvements in patient information. The labelling of certain drugs has improved. This is the case for Renaudin[®] vials of *adrenaline* and *atropine*, following harmonisation of the labelling on vials of several injectable solutions by the French drug regulatory agency in 2007. The dose strengths of *fosphenytoin* and *phenytoin* equivalent can now be more clearly distinguished on boxes of Prodilantin[®] (*Rev Prescrire* n° 201). And the total amount of *ziconotide* has been added to the front of boxes of Prialt[®] solution for infusion 100 micrograms/ml, while the international nonproprietary name (INN) has been added to the vials, albeit in small print (*Rev Prescrire* n° 316).

In contrast, no improvements were made to two products containing *isotretinoin* (Procuta[®] and Curacné[®]): the brand name still overshadows the INN of this highly teratogenic drug (*Rev Prescrire* n° 267). Similarly, boxes of Nurofentabs[®] and Nurofen-flash[®] (formerly Nuroflash[®]) do not sufficiently highlight the INN (*ibuprofen*). This creates a risk of accidental exposure during pregnancy, and also a risk of overdose, particularly during concomitant self-medication with other products containing *ibuprofen* (*Rev Prescrire* n° 264, n° 319).

Some instructions for use are now more informative, such as those for Monuril[®] (*fosfomycin*) (*Rev Prescrire* n° 103) (1). In contrast, the patient leaflets for the nonsteroidal anti-inflammatory drugs (NSAIDs) we examined in 2013 fail to highlight the risks to the fetus during the first two trimesters of pregnancy (*Rev Prescrire* n° 352; n° 340; n° 328; n° 304; n° 292).

The two-box dosing schedule printed on boxes of Flixovate[®] (*fluticasone*) cream and ointment, which exposed infants to a risk of overdose, has been removed.

Ease of use: we can and must do better. The results of our analysis of dosing devices are disappointing. One questionable improvement is the inclusion of a measuring cup graduated in millilitres for *ethosuximide* (Zarontin[®]). This is better than using a household spoon, but the cups are imprecise and unreliable, which is unacceptable for an antiepileptic drug (*Rev Prescrire* n° 309; n° 338).

The oral syringes provided with oral *levetiracetam* 100 mg/ml (Keppra[®]) are still graduated in millilitres, requiring the user to convert the dose; this is a proven source of serious dosing errors (2) (*Rev Prescrire* n° 327).

Vials of BCG SSI[®] vaccine still contain a volume equivalent to 10 or 20 doses and a syringe of inappropriate capacity, even though abscesses at the injection site have been reported following overdose (*Rev Prescrire* n° 267; n° 285).

Confusing packaging: slight improvements. The oral solution and syrup of *valproic acid* (Dépakine[®]) are easier to distinguish, with the use of different-coloured boxes and syringe plungers (*Rev Prescrire* n° 231; n° 257).

Although the packaging for Atacand[®] (*candesartan*) and Hytacand[®] (*candesartan + hydrochlorothiazide*) was slightly improved, the graphics used for these two products remain similar and are easily confused (*Rev Prescrire* n° 226183).

Presentations that trivialise drugs. The appearance of some packaging remains inappropriate. Ketum[®] 120 g gel (*ketoprofen*) still resembles a toothpaste tube (*Rev Prescrire* n° 202). Lozenges containing *flurbiprofen* (Strefen[®]), an NSAID for self-medication, still resemble candy (*Rev Prescrire* n° 281). Most *methylphenidate* tablets and capsules are still sold in bulk bottles (Concerta[®] LP, Ritalin[®] LP), making it more difficult to teach children of the need to carefully respect the prescribed dose of this amphetamine (*Rev Prescrire* n° 258).

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a- About twenty drugs that received a Red Card since 1991 are no longer marketed in France.

1- ANSM "Notice-Monuril[®] 3 g, granulés pour solution buvable en sachets" 25 October 2010: 5 pages.
2- European Commission "Leaflet-Keppra[®] 100 mg/ml, oral solution" 26 August 2013: 8 pages.