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## 2011 drug packaging review: too many dangers and too many patients overlooked



### Abstract

● Every year, *Prescrire*'s analysis of drug packaging confirms the importance of taking packaging into account in assessing a drug's harm-benefit balance.

● Safe, tried and true options are available, yet the quality of most of the drug packaging *Prescrire* examined in 2011 left much to be desired.

● Few of the packaging items examined help prevent medication errors and many actually increase the risks: misleading and confusing labelling, dosing devices that create a risk of overdose, bottles without a child-proof cap, and inadequate or dangerous patient information leaflets. Umbrella brands continue to expand and are a potential source of medication errors.

● Some patients are at greater risk: the patient leaflets for NSAIDs endanger pregnant women and their unborn babies; children are insufficiently protected by paediatric packaging and are at risk due to the lack of child-proof caps on too many bottles.

● The raft of regulatory measures taken by the French drug regulatory agency (Afssaps) in the aftermath of the Mediator<sup>®</sup> disaster overlooked the importance of packaging.

● Until drug regulatory agencies tackle the vast issue of drug packaging, it is up to healthcare professionals to protect patients from harm.

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Patients need to have easy access to high quality care. Drug packaging represents one aspect of quality care. Every year, *Prescrire* publishes a review of its systematic analyses of the packaging of the drugs examined in its "New Products" section (a). These analyses regularly lead us to issue warnings, when we identify packaging items that are a potential source of medication errors or serious incidents, although safe, tried and true options are available.

What is *Prescrire*'s verdict on the quality of the packaging it examined in 2011?

### High quality drug packaging exists

Tablets and capsules account for three-quarters of the pharmaceutical market. All that is required to package them correctly are: a brand name that includes the international nonproprietary name (INN); plain and effective labelling in which the INN and dose strength are given adequate prominence and not overshadowed by superfluous graphics; single-unit blisters, i.e. each blister pocket is labelled with the INN, dosage form, dose strength, batch number and expiry date, and is pre-cut, with each unit dose still fully labelled after separation; and a clear patient leaflet.

In 2011, only one of the medicinal products we examined satisfied all of these criteria: Mexilétine AP-HP<sup>®</sup> (*mexilétine*) (*Rev Prescrire* n° 330).

**A few interesting examples.** Single-unit blisters make it possible to clearly identify each tablet, e.g. *sirolimus* 0.5 mg - Rapamune<sup>®</sup> (*Rev Prescrire* n° 336), *amlodipine* + *telmisartan* - Twynsta<sup>®</sup> (*Rev Prescrire* n° 335) and *bilastine* - Bilaska<sup>®</sup>, Inorial<sup>®</sup> (*Rev Prescrire* n° 338). Some blister packs are sealed with a safety ►►

a- For additional information on *Prescrire*'s Packaging Working Group and on technical terms such as "single-unit blister" and "dosing schedule", and to read our previous annual drug packaging reviews: for the French version, select "Les Cahiers *Prescrire*" from the "Libre accès" drop-down menu at [www.prescrire.org](http://www.prescrire.org), then select "Le conditionnement des spécialités pharmaceutiques"; for the English version, search for the term "packaging" at <http://english.prescrire.org/en/>. The 2011 packaging review builds upon *Prescrire*'s previous annual reviews and our responses to certain public consultations on drug packaging.

► film, making it difficult for young children to gain access to the tablets or capsules inside the blister pockets, e.g. *miglustat* - Zavesca° (Rev Prescrire n° 328) and *bosentan* 32 mg - Tracleer° (Rev Prescrire n° 329). The outer surface of the medicated plaster *lidocaine* - Versatis° (Rev Prescrire n° 330) is directly labelled with its INN and dose strength: a rare but welcome feature.

The INN *progesterone* is displayed in a central position in large lettering on the front of the outer packaging of the brand-name generic drug Progestan° (Rev Prescrire n° 333). Several generic manufacturers have made a similar effort (b).

The outer packaging also sometimes displays useful warnings. For example, the outer packaging of the oral immunosuppressant *methotrexate* - Novatrex° (Rev Prescrire n° 331) has a centrally positioned warning that the drug is not to be taken every day. The message is repeated on the bottle cap, which unfortunately is not child-proof.

Only a minority of multidose bottles containing oral liquid formulations have a child-proof safety cap, e.g. *valsartan* - Tareg° (Rev Prescrire n° 338) and *paracetamol* - Doliprane°, Dafalgan° (Rev Prescrire n° 334).

**Several improvements.** We noticed several improvements in 2011: *ustekinumab* - Stelara° (Rev Prescrire n° 327) now only comes in prefilled syringes with a needle stick protection device, rather than in bottles; *terlipressin* - Glypressine° is now available as a ready-to-use solution as well as in the form of a bottle of powder + solvent (Rev Prescrire n° 328); *ritonavir* - Norvir° tablets can be stored at room temperature, so are more convenient than the older capsules that required refrigeration (Rev Prescrire n° 331); the *etonogestrel* implant - Nexplanon° comes with an applicator for easier, safer insertion and is also easier to locate for removal (Rev Prescrire n° 332); more prefilled syringes containing injectable drugs are equipped with a needle stick protection device, e.g. *darbepoetin alfa* - Aranesp° and *pegfilgrastim* - Neulasta° (Rev Prescrire n° 333) and *alteparin* - Fragmine° 2500 IU and 5000 IU (Rev Prescrire n° 335); the first *somatropin* multidose prefilled pen - Norditropine Nordiflex° (Rev Prescrire n° 335) is a ready-to-use option (but must be refrigerated).

**Other improvements are only relative.** The ready-to-use solution and prefilled syringe forms of *omalizumab* - Xolair° (Prescrire Int n° 121) are more convenient than the former bottle of powder + solvent, but should still be avoided due to the drug's unfavourable harm-

benefit balance. *Romiplostim* - Nplate° (Rev Prescrire n° 332) now comes with the devices required for its preparation, but the labelling of its dose strength remains a potential source of confusion.

### Identify misleading and confusing labelling before errors occur

The usual labelling flaws were particularly pronounced in 2011.

**INNs absent or barely legible.** The INN is a drug's true name, yet it was not mentioned on the labelling of several blister packs: *racecadotril* - Diarfix° (Rev Prescrire n° 328); *meprobamate* + *aceprometazine* - Mépronizine° (Rev Prescrire n° 333) until its withdrawal from the French market in January 2012; *quinine* + *thiamine* - Hexaquine° (Rev Prescrire n° 337) (c); Timothy grass (*Phleum pratense*) pollen extract - Grazax° (Rev Prescrire 328). The single-dose containers of *levocabastine* - Levofree° eye drops only display the brand name, in lower-case lettering, which can be rubbed off with a finger (Rev Prescrire n° 328).

When the INN is present (which is mandatory), it is commonly not given adequate prominence: it is barely legible on the embossed, shiny film of the blister pack of the *ethinylestradiol* + *levonorgestrel* generic Lovavulo° (Rev Prescrire n° 327), and printed in tiny lettering on the blister pack of *tianeptine* - Stablon° (Rev Prescrire n° 337) and *Actifedsign*° (*paracetamol* + *chlorphenamine* + *vitamin C*) (Rev Prescrire n° 338). On some outer packaging, the INN is printed underneath the brand name as if simply to underline it, e.g. *isothipendyl* - Apaisylgel° (Rev Prescrire n° 335), injectable *cloxacillin* - Orbénine° (Rev Prescrire n° 336) and *mequitazine* - Primalan° (Rev Prescrire n° 337).

Sometimes the INN and dose strength are difficult to read due to insufficient contrast with the background: yellow print on the aluminium film of blisters containing *octreotide* 0.1 mg - Siroctid° (Rev Prescrire n° 332); pale pink on white blisters containing *morniflumate* suppositories - Nifluril Enfants° (Rev Prescrire n° 336); white print against a yellow background for *paracetamol* oral solution - Dolko° (Rev Prescrire n° 334).

**INNs printed separately from dose strengths.** Most labelling conforms to a layout that separates the INN from its dose strength, in accordance with regulations. For example, the box and bottle of *Daivobet*° (Rev Prescrire n° 331) display the following information, from top to bottom:

– the brand name;

– the dose strength as “50 micrograms/0.5 mg/g”;

– the term “gel”;

– then the INNs “*calcipotriol/betamethasone*”.

Yet it would be more logical and, more importantly, less conducive to medication errors if each INN were displayed next to its dose strength. In the example cited above: “*calcipotriol* 50 micrograms/g” and “*betamethasone* 0.5 mg/g”.

**Stickers to warn users of a change: advantages and limitations.** In 2011, changes were made to the marketing authorisations (MAs) for injectable *oxacillin* - Bristopen° (Rev Prescrire n° 336) and *mequitazine* - Primalan° (Rev Prescrire n° 337). In the first case, intramuscular administration was no longer authorised; in the second, the drug was no longer available without a prescription. The outer packaging examined had already been manufactured at the time of the MA variation; therefore, the new information was added to the boxes in the form of a sticker. However, the contents of the boxes, the internal labelling and patient leaflet were not modified, creating a risk of error due to contradictory information. It is imperative that all packaging items be rapidly updated after changes in the marketing authorisation. If it would compromise access to the drug in the short term to withdraw batches that were manufactured before the variation or that are already stocked in pharmacies, measures to modify the packaging already present on the market must be comprehensive: all of the outer and inner labelling must be amended and an up-to-date patient leaflet provided.

**Dangerous proliferation of pictograms and dosing schedules.** Colokit° tablets of sodium phosphate salts are used to cleanse the bowel before a colorectal investigation. The patient leaflet includes a comprehensive, detailed dosing schedule (see footnote a on page 133) explaining when to administer the 8 doses, each consisting of 4 tablets taken with 250 ml of water, i.e. 32 tablets in total. Taking the tablets with a large volume of water is crucial, because the drug can cause renal damage and sometimes fatal electrolyte disturbances. However, the outer packaging shows a different dosing schedule, consisting of only 2 dose squares along with some other ►►

b- Many generic products prominently display the INN. However, readers have pointed out that some graphic designs used on the outer packaging of different products from the same manufacturer can lead to confusion (Rev Prescrire n° 337).

c- The company has announced that its new blister packs will be labelled with the INNs.



## Drug packaging: improvements needed to protect children

When adapting a drug for paediatric use, its packaging must also be adapted (a,b).

*Prescrire*'s review of the packaging it examined in 2011 shows that many improvements must still be demanded of drug regulatory agencies and provided by pharmaceutical companies. And until these improvements materialise, it is up to healthcare professionals to prevent medication errors.

**The European Paediatric Regulation: few positive effects as yet.** *Losartan* - Cozaar<sup>®</sup> was authorised for the treatment of hypertension in children in 2009 (*Prescrire Int* n° 108). The paediatric oral suspension was introduced to the market 17 months later and is not reimbursed by the French national health insurance system (*Rev Prescrire* n° 329). Difficulties are anticipated as a result of its packaging: the suspension is not ready to use; the materials provided for its reconstitution are conducive to error; the oral dosing syringe provided is graduated in millilitres, and calculations to convert the milligrams prescribed into the equivalent volume measured are a potential source of error.

Despite these flaws, *losartan*'s market monopoly has been extended by 6 months in France, under the European Paediatric Regulation that came into effect in 2007 (c). In the case of *losartan*, the drug company has profited, but children have not benefited (d). One of the main objectives of the European Paediatric Regulation is to improve the convenience of treatments administered to children: the European Medicines Agency should set higher standards when implementing this regulation (1).

The packaging for the second paediatric angiotensin II receptor blocker to be marketed in 2011 is of higher quality (*valsartan* oral solution - Tareg<sup>®</sup>; *Rev Prescrire* n° 338). The solution does not require reconstitution. The outer packaging contains two dosing devices, an oral delivery syringe and a graduated cup, a sensible but unusual step. Although detailed instructions are provided in the package leaflet, it is advisable that healthcare professionals explain to parents how to use them. The syringe and cup are graduated in millilitres rather than in milligrams of *valsartan*.

**Poor quality packaging is still common: risk of overdose or treatment failure.** In 2011, we re-examined the oral liquid paediatric forms of *paracetamol* available in France (*Rev Prescrire* n° 334). Dolko<sup>®</sup> had the worst packaging: the bottle has no child-proof cap and the INN and dose strength on the labelling are difficult to read. The packaging of the other two paediatric *paracetamol* oral liquid preparations (Dafalgan<sup>®</sup> and Doliprane<sup>®</sup>) was also flawed.

In 2011, the French drug regulatory agency re-examined antitussives for children, but no measures were taken to improve their packaging. Yet most antitussives have poor quality packaging: most come without a dosing device or with a graduated cup that carries a risk of overdose; too many bottles lack a child-proof cap. In addition, their patient leaflets do not explain the natural course of normal, mild cough, the fact that the therapeutic value of the drug has not been demonstrated, or the non-drug options available. The provision of a child-proof cap, an accurate, suitable oral delivery syringe and an informative patient leaflet would better protect children, who unfortunately will remain exposed to the adverse effects of the antitussives that have been kept on the French market.

The paediatric packaging for *metoclopramide* oral solution was modified in 2011 but remains of mediocre quality (*Rev Prescrire* n° 328): there is no child-proof cap, the syringes are graduated in kilograms of body weight, and the syringe for babies is difficult to read (e)(2).

*Sodium picosulfate* powder - Picoprep<sup>®</sup> is used to cleanse the bowel before an investigational procedure (*Rev Prescrire* n° 330). The 2011 patient leaflet stipulated that one-quarter or half of a sachet should be administered to children, according to age (3). But the leaflet does not provide any advice on how to accurately prepare a quarter or half dose. This packaging flaw exposes children to a risk of dangerous overdoses or failed bowel investigations (f).

**Better protection for children.** In 2011, children were not adequately protected from the dangers of drugs, excipients and medication errors. The risks are greater still when they are treated with products that are not approved for paediatric use but are nevertheless commonly administered to children. The current pharmaceutical market is too dangerous. And the effects of the European Paediatric Regulation are still insufficient.

In 2011, the European Medicines Agency (EMA) released a draft guideline on the development of paediatric drugs for public consultation (4). It provides an opportunity to introduce stricter requirements to better protect children. *Prescrire* responded to the public consultation to improve weaknesses in the draft guideline with respect to packaging and excipients (4,5).

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a- See pages main text for more information about protecting children from the risks posed by drugs not intended for paediatric use.

b- When adapting drugs to paediatric use, the formulation must also sometimes be changed. For example, in 2011, the US Food and Drug Administration (FDA) blamed the excipients of the oral solution lopinavir + ritonavir - Kaletra<sup>®</sup> for serious adverse effects that occurred in preterm and full term newborn babies: the high alcohol content (42%) inhibits the metabolism of propylene glycol, with the risk of accumulation to levels that are toxic in this age group (*Rev Prescrire* n° 332). This medicine is not recommended for children under the age of 2 years but it is often used, due to its antiretroviral efficacy. Yet the pharmaceutical company has not marketed any products that are suitable for this age group.

c- The European Paediatric Regulation provides 6 months of supplementary protection (and therefore market monopoly) for drugs intended for use in adults if the company that markets them meets the obligations set out by the European Medicines Agency concerning paediatric drug development.

d- According to the figures of the French national health insurance fund for salaried workers (Cnamts) on reimbursement requests during 2009, reimbursements for *losartan* (excluding the *losartan* + hydrochlorothiazide combination) over a 6-month period totalled 27 million euros (refs 1,6).

e- As of late 2011, in the wake of the European harmonisation of the paediatric information for *metoclopramide*, the French drug licensing committee recommended banning its use in children (ref 2).

f- The drug company says that it expects to obtain authorisation in 2012 to provide a dose-measuring spoon for measuring quarter and half doses.

### Selected references from *Prescrire*'s literature search

1- "Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004" *Official Journal of the European Union* 27 December 2006: L 378/1-L 378/19.

2- Affsaps "Point d'information sur les dossiers discutés en commission d'AMM. Séance du 13 octobre 2011" 14 octobre 2011: 3 pages.

3- Affsaps "Notice-Picoprep" 31 janvier 2011: 7 pages.

4- Agence européenne du médicament "Draft. Guideline on pharmaceutical development of medicines for paediatric use" 19 mai 2011: 23 pages.

5- *Prescrire* Editorial Staff "Prescrire's response to the public consultation on EMA/CHMP/QWP/180157. "Draft. Guideline on pharmaceutical development of medicines for paediatric use"" 29 December 2011: 10 pages.

6- Cnamts "Cozaar<sup>®</sup>". In: "Medic'am 2004-2009" juin 2010 (ameli.fr): extraction papier 1 page.



► information. Users who read this dosing schedule but not the patient leaflet could take the wrong number of tablets at the wrong frequency, potentially resulting in an overdose (*Rev Prescrire* n° 329).

In 2011, Pérubore° tablets for inhalation (*essential oils of lavender, rosemary and red thyme + thymol*) (2 tablets per dose) were replaced by capsules containing twice the dose (1 capsule per dose). The small dosing schedule on the outer packaging of Pérubore° for inhalation (*Rev Prescrire* n° 335) has an illustration of 2 capsules and a pair of scissors. It is not readily obvious that the 2 capsules are separated by the word “or” in small print that barely stands out against the background. The 2 capsules actually illustrate 2 alternative preparation methods: either the capsule is placed in hot water, or the tip of the capsule is cut and its contents poured into the water. Patients who had previously been using 2 tablets could be confused by this dosing schedule and use 2 capsules, resulting in an overdose.

The pictogram on the single-dose containers of cutaneous *chlorhexidine* - Septidose° (*Rev Prescrire* n° 336) shows a row of 4 boxes in increasingly lighter shades of green. The first shows a large-headed child of indeterminate age, the second probably represents an adult, the third depicts two superimposed single-dose containers, and the fourth is empty. What is the intended message? The drug company could have made better use of this space by increasing the INN and route of administration on the labelling, in order to prevent confusion with the plethora of similar single-use containers marketed for use in babies, including hygiene products and physiological saline. Dangerous errors involving these types of containers have already occurred, in which the wrong route of administration was used (*Rev Prescrire* n° 284 and n° 326).

Dosing schedules and pictograms are used to convey complex information. It would be better to reserve their use for essential messages and to conduct comprehension tests among patients and pharmacists before they are displayed on marketed products.

**Umbrella brands: a growing problem.** Medicines containing very different active ingredients can be marketed under the same umbrella brand. Their packaging includes prominent graphics designed to be easily recognisable by users. But these graphics make very different medicines look alike, with the potential for confusion and medication errors. Umbrella brands gain ground every year, for example the “Doli” product line,

which expanded again in 2011 (*Rev Prescrire* n° 331) as well as the Vicks product line (*Rev Prescrire* n° 338).

Some cold remedies are authorised when a number of symptoms coexist, such as fever, nasal discharge, headache and watery eyes. But these symptoms are sometimes mentioned separately on the front of the box, as optional alternatives. For example, the labelling on the boxes of Actifed états grippaux° (*Rev Prescrire* n° 332) and Actifedsign° (*Rev Prescrire* n° 338) (*paracetamol + chlorphenamine + vitamin C*) implies that these medicines are suitable for the treatment of an isolated symptom, such as fever. However, in this case, *paracetamol* alone would be a more appropriate choice.

*Oxememazine* of the Humex° product line (*Rev Prescrire* n° 337) is a shocking example of inappropriate, umbrella-brand packaging. This phenothiazine antihistamine syrup is marketed in a bottle without a child-proof cap. The box contains a measuring cup, a dosing device known in practice to carry a risk of overdose. The outer packaging and bottle show a caramel liquid that resembles a creamy dessert. The term “night-time” is prominently displayed next to a moon on a midnight blue background. It is easy to assume that this is a treatment for insomnia, yet that is not its approved indication.

The graphics on the box of the antihistamine *niaprazine* - Nopron° were amended after the French drug regulatory agency noticed a starry, midnight blue sky that trivialised the use of an antihistamine in childhood insomnia (*Rev Prescrire* n° 243).

### No outer packaging: a trend to be monitored

The outer packaging is an excellent medium for clearly displaying important information about the drug (INN, dose strength, route of administration, storage conditions). It is by definition larger than the items it contains and a higher level of contrast is possible than on a transparent bottle or a metallic blister pack. It also protects the drug from light and variations in temperature when necessary. It is also a reliable way of keeping the dosing devices and patient leaflet with the drug.

Two types of product packaging for the over-the-counter mouthwash Eludrilpro° (*chlorhexidine + chlorobutanol*) (*Rev Prescrire* n° 338) have been authorised without a box. The dosing device, a cup, fits over the neck of the bottle. The text for the patient leaflet is printed in small white letters on a transparent label around the bottle; it is difficult to read on the 200-ml bottle. It is worth reading

though, to learn that the solution contains 42.8% alcohol, for example.

A drug without outer packaging is cheaper to produce. It may appear practical and more environmentally friendly, but the quality of the examples examined in 2010 and 2011 left much to be desired.

### Too many bottles are easily opened by children

The three oral forms of *methotrexate* available in France come in bulk bottles without a child-proof cap (*Rev Prescrire* n° 331). Yet massive ingestion of this cytotoxic drug could be fatal for a child.

Bottles of candy-pink *betamethasone + dexchlorpheniramine* tablets - Célestamine° are closed with a simple stopper, of the sort found on tubes of *aspirin* in the last century (*Rev Prescrire* n° 331). *Perindopril arginine* 10 mg + *indapamide* 2.5 mg - Bipreterax° comes in the same type of bottle (*Rev Prescrire* n° 327), as does the *quinine + crataegus* (dry hawthorn extract) combination Okimus° (*Rev Prescrire* n° 337), which contains a sufficient quantity to kill a child.

The following drugs come in bottles with easily unscrewed caps: *metoclopramide* paediatric oral solution - Prim-péran° (*Rev Prescrire* n° 328); the opioids *pholcodine* - Flucalyptol toux sèche pholcodine° (*Rev Prescrire* n° 327 and n° 333) and *dextromethorphan* - Euphonyll° (*Rev Prescrire* n° 330); the antiepileptic *ethosuximide* - Zarontin° (*Rev Prescrire* n° 338); the benzodiazepines *clonazepam* - Rivotril° (*Rev Prescrire* n° 337) and *diazepam* - Valium° (*Rev Prescrire* n° 338); and *mequitazine* - Primalan° (*Rev Prescrire* n° 337).

Like Eludrilpro°, the *chlorhexidine + chlorobutanol* mouthwash - Buccosoin° (*Rev Prescrire* n° 335) comes in a bottle with no child-proof cap and contains a high proportion of alcohol (42.8%).

Until drug regulatory agencies systematically address the risks associated with children ingesting drugs and safeguard the public by imposing stricter MA requirements, we must all follow a few basic rules: keep drugs and drug waste out of the reach of children, and take care not to drop any tablets from bulk bottles.

### Dosing devices: delicate situations

Almost all of the dosing devices examined in 2011 were flawed or even dangerous. The labelling of *memantine* oral solution - Ebixa° has improved, but the dosing pump on the bottle must be primed before use, which remains a source of error (*Rev Prescrire* n° 328); in any case,

## Rebuilding regulation after the Mediator<sup>o</sup> disaster: drug regulatory agencies must tackle the issue of packaging

The Mediator<sup>o</sup> disaster led to a major shake-up within the French drug regulatory agency in 2011 (see *Prescrire Int* n° 126 page 110). But the issue of packaging was overlooked in the raft of regulatory measures taken in 2011.

**Packaging, the poor relation in drug re-assessments.** For example, when commonly used paediatric drugs such as anti-tussives were re-assessed in France, their packaging was not questioned, although for the most part, it is dangerous (see inset page 135). Similarly, when *pholcodine* was reclassified as a prescription-only drug, no improvements in the packaging were imposed (see inset *Prescrire Int* n° 126 page 108).

The decision to improve the labelling of oral forms of *methotrexate* is a welcome move, but other aspects of the packaging of the drugs concerned remain unsafe. A better alternative to dangerous bulk bottles must be demanded, such as blister packs with a safety film and a device to help patients with limited dexterity remove tablets or capsules from the blister pockets.

As of 2011, *quinine* is unfortunately still marketed for cramps in France. Fewer patients will be exposed to its adverse effects now that it is no longer reimbursed by the French national health insurance system, but some patients will continue to be at risk (*Rev Prescrire* n° 337). The patient leaflets for the products concerned still do not inform patients about adverse effects, the bottle for *Okimus<sup>o</sup>* still has no child-proof cap, and blister packs containing *Hexaquine<sup>o</sup>* are still not labelled "*quinine*" (a).

The reclassification of *mequitazine* as a prescription-only drug does not alter the fact that the bottle is still not equipped with a child-proof cap and that a dose-measuring spoon is less accurate than a suitable oral delivery syringe (*Rev Prescrire* n° 337).

Restricting the prescription of *clonazepam* - *Rivotril<sup>o</sup>* does not alter the fact that the bottle has no child-proof cap, that a dropper is a less efficient dosing device than a suitable oral delivery syringe. In addition, the blister pack and patient leaflet

for these tablets are difficult to read (*Rev Prescrire* n° 337).

**Umbrella brands: evidence of the authorities' lax attitude towards packaging.** The current state of the pharmaceutical market gives the impression that the French and European regulatory agencies are too often following the lead of drug companies on the issue of packaging quality, especially concerning 'umbrella' brands in the self-medication sector. In 2011, a ban on umbrella brands was still not forthcoming, and the problem continued to worsen with the authorisation of an *oxomemazine* product in a bottle with no child-proof cap, a dosing device (cup) liable to cause overdose, and unnecessarily fanciful labelling (*Rev Prescrire* n° 337).

### Differences between originator drugs and generics: a matter for regulators.

Differences in dose strengths, concentrations and product packaging between originator drugs and generic versions are a potential source of medication errors. For example, a change in the formulation of originator drugs containing *perindopril* led to a difference in the expression of dose strength from that of the generic versions, creating a risk of overdose (*Rev Prescrire* n° 316 and n° 327). Risks are likely now that the dosage form and concentration of *docetaxel* - *Taxotere<sup>o</sup>* (*Rev Prescrire* n° 327) differ from generic versions. In 2011, a generic drug containing *lidocaine* + *adrenaline* was considered conducive to error because the concentration of *adrenaline* differed from that of the originator drug (1).

Drug regulatory agencies have a responsibility to focus first and foremost on patient safety in their decision-making and should anticipate practical differences between originator drugs and generics.

**An initial reaction from the French agency in 2011.** During the past year, *Prescrire* received a letter from the French agency responding to our 2010 packaging review (2). According to this letter, the agency is examining the cases presented in the review.



Furthermore, the French agency's project to re-assess marketing authorisations granted before 2005 will hopefully lead to the withdrawal of drugs with a negative harm-benefit balance, thus avoiding the need to modify their dangerous packaging. For drugs that are kept on the market, the project should place greater emphasis on packaging (3).

### Analysing successes and failures.

More generally, drug regulatory agencies should make a careful study of the pharmaceutical sector, specifically focusing on the issue of packaging, in order to identify successes as well as failures. They would then be able to guide pharmaceutical companies with full knowledge of the facts, so that they all develop safe, appropriate packaging, focusing first and foremost on the interests of the various types of patients who use their drugs.

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a- The pharmaceutical company has announced that a blister pack labelled with INNs will soon be available.

### Selected references from Prescrire's literature search

- 1- Afssaps "Différence de concentration en adrénaline entre la Lidocaïne Aguetant Adrénaline et Xylocaïne Adrénaline" avril 2011: 1 page.
- 2- Afssaps "Bilan 2010 du conditionnement paru dans *Prescrire* de février 2011" Courrier à *Prescrire* 8 août 2011: 2 pages + réponse de *Prescrire* 1 septembre 2011: 2 pages.
- 3- *Prescrire* "Permettre l'examen simplifié des modifications des termes des AMM purement nationales ? Oui, mais d'abord réévaluer les "vieilles AMM" nationales" Response to the public consultation of the European Commission 21 October 2011: 4 pages.

this drug is best avoided. Doses of *ethosuximide* - *Zarontin<sup>o</sup>* (*Rev Prescrire* n° 338) no longer have to be measured with an ordinary spoon, but the measuring cup that is now provided is a poor choice, since cups are known in practice to lead to overdose. As of late 2011, nasal *fentanyl* -

*Instanyl<sup>o</sup>* was still marketed in dangerous multidose bottles with a dosing pump. Slightly less dangerous single-dose bottles became available at the end of 2011, but only in hospitals (*Prescrire Int* n° 123).

Droppers are still marketed: *diazepam* - *Valium<sup>o</sup>* (*Rev Prescrire* n° 338) and *clona-*

*zepam* - *Rivotril<sup>o</sup>* (*Rev Prescrire* n° 337). A welcome feature is a diagram on the opening tab of their outer packaging, showing that the dropper should be held vertically during use. Failing the provision of an accurate, suitable oral delivery syringe, it is high time that patient ►►



► leaflets include information and diagrams on the proper use of droppers.

The oral delivery syringe for Vitamin K1 Roche nourrissons° 2 mg oral or injectable solution (*phytomenadione*) was one of the rare examples examined of an oral syringe graduated in milligrams, but it includes a superfluous 1-mg graduation that could create confusion (*Rev Prescrire* n° 337); according to the summary of product characteristics (SPC), the 1-mg dose is only administered by injection.

### Patient leaflets: inadequate and dangerous

Package leaflets developed through European centralised MA procedures have shown a trend towards overall improvement in recent years, e.g. *telaprevir* - Incivo° (*Rev Prescrire* n° 339). But more progress is needed. One serious flaw is that brand names too often take precedence over INNs. Patient leaflets should explain that the INN is a drug's true name and encourage patients to remember INNs to facilitate their discussions with healthcare professionals and to be able to identify their drugs in the interactions sections of other patient leaflets, for example.

However, the patient leaflets for many older drugs that were approved through non-centralised procedures are inadequate.

For example, the patient leaflet for *flumetasone* + *salicylic acid* + *coal tar* - Alkotar° (*Rev Prescrire* n° 337) does not explain the uncertainty over the potential carcinogenic effect of *coal tar* (1).

As of 19 December 2011, the patient leaflet available on the French agency website for *mephenesin* + *methyl nicotinate* ointment - Décontractyl° (*Rev Prescrire* n° 328 and n° 337) still did not contain a warning about the risk of acute generalised exanthematous pustulosis reported in 2011 (2).

The patient leaflet for *quinine* + *thiamine* - Hexaquine° (*Rev Prescrire* n° 337) does not reflect the disproportionate risks associated with *quinine*, which include cardiac disturbances and prolongation of the QT interval that increase the risk of torsades de pointes, as well as hypoglycaemia and renal failure (3).

The leaflet for *tianeptine* - Stablon° (*Rev Prescrire* n° 337) does not mention its hepatic risks (4).

**NSAIDs and pregnancy: enough is enough!** The data on NSAIDs suggest that their administration during the first trimester of pregnancy increases the risks of miscarriage and malformations. If they are taken after the first trimester, NSAIDs

expose the fetus to serious and sometimes fatal cardiovascular and renal risks (*Rev Prescrire* n° 301).

However, in the patient leaflets examined in 2011, regardless of dosage form and legal status, NSAIDs were only clearly contraindicated from the sixth month of pregnancy.

The products concerned are: oral *keto*-*profen* - Bi-Profénid LP° and Profemigr° (*Rev Prescrire* n° 327), oral *ibuprofen* + *codeine* - Antarène Codéine° (*Rev Prescrire* n° 332), oral *ibuprofen* + *pseudoephedrine* - Adviltab rhume° (*Rev Prescrire* n° 332); *diclofenac* + *heparin* medicated plasters - Flector Tissugel Héparine° (*Rev Prescrire* n° 329); *diclofenac* gel - Compralfène° and Tendol° (*Rev Prescrire* n° 336), *morniflumate* suppositories - Nifluril enfants° (*Rev Prescrire* n° 336), and *diclofenac* suppositories - Voltarène enfant° (*Rev Prescrire* n° 338) (5-13).

The patient leaflet for *mesalazine* sustained release tablets - Mezavant LP° (*Rev Prescrire* n° 332) is more informative and states: "(...) *mesalazine crosses the placenta in pregnancy (...), due caution should be taken (...) in pregnancy*". The stated daily dose is 2.4 g to 4.8 g (14). However, according to the SPC for *mesalazine* - Pentasa° (*Rev Prescrire* n° 271) published on the French agency website and dated 6 January 2011 (our translation) "*at doses greater than 2 g per day, the plasma concentrations of the salicylate mesalazine could expose the fetus to the risk of adverse effects, particularly renal effects (NSAID effects)*". It also states that "*one case of fetal renal damage (...) and renal failure at birth was reported with administration of oral mesalazine 4g/day during the second trimester of pregnancy*" (15).

NSAIDs are best avoided throughout pregnancy to avoid exposing the unborn child to any risks. A clear message to this effect in patient leaflets would benefit pregnant women.

**More readability tests needed.** Some patient leaflets lack important information.

For example, the patient leaflet for injectable *iron* - Venofer° (*Rev Prescrire* n° 331) does not mention that it must be diluted before injection. It would be better to follow the preparation instructions in the SPC.

None of the patient leaflets for the antitussives examined in 2011 described the natural course of cough or the non-drug options for relieving symptoms.

An explanation of the disorders associated with *vitamin B1* deficiency would improve the leaflet for Bénerva° (*Rev Prescrire* n° 336) (16).

The leaflet for *fosfomycin trometamol* - Monuril° (*Rev Prescrire* n° 335) does not

inform patients that in young women who are not pregnant, half of all cases of uncomplicated lower urinary tract infections resolve spontaneously within weeks without treatment. Nor does it explain that 20% to 25% of cases of uncomplicated acute cystitis resolve spontaneously within 48 hours without antibiotic therapy (*Rev Prescrire* n° 330) (17).

Wider application of readability tests among target patient groups or even healthcare professionals would result in more effective patient leaflets. It would also rid them of simplistic statements such as the one (our translation) from the patient leaflet for the antineoplastic *bleomycin* - Bléomycine Teva° (*Rev Prescrire* n° 335): "(...) *normal cells are less sensitive to bleomycin than tumour cells. They will therefore survive whereas tumour cells will be destroyed*" (18).

### In summary

These shortcomings and flaws in drug packaging undermine the efficacy of treatments and patient safety. They show that convenience of use must be taken into account when evaluating drugs prior to authorisation and during their re-assessment.

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### Selected references from Prescrire's literature search.

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- 2- Afssaps "Notice-Décontractyl baume" 13 juillet 2010: 6 pages.
- 3- Afssaps "Notice-Hexaquine°" 15 juin 2007 : 5 pages + "Notice boîte" 30 novembre 2004: 2 pages.
- 4- Afssaps "Notice-Stablon°" 2 mai 2011: 6 pages + "Notice boîte" août 2008: 2 pages.
- 5- Afssaps "Notice-Bi-Profénid°" 19 juillet 2011: 8 pages + "Notice boîte" janvier 2010: 2 pages.
- 6- Afssaps "Notice-Profémigr°" 13 juillet 2010: 8 pages.
- 7- Afssaps "Notice-Antarène Codéine°" 14 septembre 2011: 9 pages + "Notice boîte" 14 décembre 2010: 2 pages.
- 8- Afssaps "Notice-Flector Tissugel Héparine°" 12 novembre 2010: 7 pages + "Notice boîte" août 2010: 2 pages.
- 9- Afssaps "Notice-Rhinadviltab°" 22 septembre 2011: 8 pages + "Notice boîte-Adviltab Rhume°" 20 avril 2010: 4 pages.
- 10- Afssaps "Notice-Compralfène°" 16 août 2010: 6 pages.
- 11- Afssaps "Notice-Tendol°" 28 octobre 2010: 6 pages + "Notice boîte" 14 mai 2010: 2 pages.
- 12- Afssaps "Notice-Nifluril Enfants suppositoire sécable°" 23 août 2010 : 6 pages + "Notice boîte" 22 octobre 2004: 2 pages.
- 13- Afssaps "Notice-Voltarène Enfant suppositoire°" 1<sup>er</sup> août 2005: 6 pages + "Notice boîte" juin 2003 : 4 pages.
- 14- Afssaps "Notice-Mezavant° LP" 12 mai 2011: 7 pages.
- 15- Afssaps "RCP-Pentasa 1 g comprimé°" 6 janvier 2011: 5 pages.
- 16- Afssaps "Notice-Bénerva° 100 mg/1 ml°" 12 mars 2010+ "Notice Bénerva° 500 mg/5 ml°" 14 décembre 2010: 10 pages.
- 17- Afssaps "Notice-Monuril°" 25 octobre 2010: 6 pages.
- 18- Afssaps "Notice-Bléomycine Teva°" 29 avril 2010: 8 pages.