Prescrire's review of drug packaging in 2023: reconciling ease of use with safety is an ongoing challenge

- Prescrire examined the packaging of about 220 medicinal products in 2023. As in previous years, we noted recurrent flaws, but also a few positive developments.
- If patients are to be clearly informed about their drug treatments, the international nonproprietary name (INN) of the active substance or substances present must be easily identifiable on each packaging component.
- In France, pharmaceutical companies must display a warning pictogram on the packaging of teratogenic or fetotoxic drugs, but the chosen pictogram does not always afford sufficient protection to women who are or could become pregnant.
- AQR code was printed on the box and patient leaflet of certain products, providing access to additional information and videos, published online. This online content highlights certain precautions or adverse effects, but it must not replace the more comprehensive information provided in the patient leaflet or the essential information printed on the packaging.
- Ease of use is a crucial aspect of drug packaging, as it helps ensure that the drug is used effectively, appropriately and safely. For certain injectable drugs, several injections are required in order to administer the full dose, which is both uncomfortable and inconvenient.
- Packaging also plays a crucial role in reducing the risk of errors associated with drug administration. The presence of empty blisters in a blister pack can confuse patients and their caregivers. The drug's dose strength must be clearly identifiable to reduce the risk of wrongdose errors.

• Some products are authorised for paediatric use, but are not marketed in a form suitable for young children. A few products were improved to reduce the risk of children accessing dangerous substances, for example by no longer marketing tablets in a multidose bottle, or by adding a child-resistant film to a blister pack, a child-resistant cap to a bottle, or a lock-out system on a nasal spray.

rescrire examined the packaging of about 220 pharmaceutical products featured in our French edition, *La Revue Prescrire*, over the course of 2023. Drug packaging can be considered high quality if it makes the drug safer and easy to use, and if it is designed to protect people who come into contact with the patient from the risk of poisoning, especially children. What packaging flaws and advances did we identify in 2023 on analysing the packaging of these 220 products?

Clear information to protect patients

Patients, their caregivers and health professionals need clear information about pharmaceutical products. An essential part of this is to give due prominence to the international nonproprietary name (INN) of the active substance or substances on both the box (secondary packaging) and the primary packaging, i.e. the container in direct contact with the drug, such as the bottle, vial or blister pack. Information essential for patient safety must also be displayed on the box, in the form of warnings or certain pictograms.

INNs still often overshadowed by brand names.

The INN was still printed in much smaller characters than the brand name on the packaging of many of the medicines we analysed in 2023. This carries a risk that patients, caregivers and health professionals will be unaware of the substances contained in the products concerned, and therefore of their potential harms. It can lead to confusion between products, in particular those sold under the same "umbrella" brand.

In 2023, as in previous years, INNs were often more prominent on the packaging of products authorised through the European centralised procedure than on those authorised through France's national procedure (1).

Warning pictogram concerning pregnancy: a crucial measure, imperfectly implemented. Since 2017, in France, if a drug's summary of product characteristics (SmPC) mentions a risk of teratogenicity or fetotoxicity, a specific pictogram to inform patients and health professionals of this risk must be displayed on the box, accompanied by further details where appropriate (2). As of 2024, it is left up to the pharmaceutical company concerned to choose which pictogram to display and to add any further details.

The "danger" pictogram (an illustration of a pregnant woman inside a red triangle) discourages women from using the drug just before or during pregnancy, unless no alternative treatment exists. The "prohibited" pictogram (an illustration of a pregnant woman inside a red circle, crossed out by a diagonal line) instructs women to never use the drug just before or during pregnancy; this pictogram is compulsory if pregnancy is listed as a contraindication in the SmPC in force.

These pictograms are sometimes accompanied by a statement specifying the women concerned or the period of pregnancy at particular risk. When there is doubt over which of the two pregnancy pictograms applies, the company should opt for the more restrictive "prohibited" pictogram (3). Nonsteroidal anti-inflammatory drugs (NSAIDs) should display a "prohibited" pictogram so that women are not only protected from these drugs' adverse effects from the sixth month of pregnancy, as required by current regulations, but throughout pregnancy, to also help protect them from the documented risks of NSAID use in early pregnancy.

The SmPCs for the *metopimazine*-containing products marketed in France state that, in the absence of usable clinical data, these drugs must be used with caution in women who are pregnant or breastfeeding. One such product, Vogalib°, available without a prescription, rightly features the "danger" pictogram on the box, while other prescription-only products, such as Vogalène Lyoc° and Métopimazine Venipharm°, do not. Pharmaceutical companies can therefore choose different pictograms for their boxes, based on the same teratogenicity or fetotoxicity data, which is confusing for healthcare professionals and patients alike.

One pharmaceutical company took the initiative of adding a useful statement alongside the "prohibited" pictogram on the box of its *methotrexate*-containing product Novatrex°, to also warn against its use in breastfeeding women, and men and adolescents of childbearing age.



The warning pictogram on boxes of Novatrex* (methotrexate):

NOVATREX + PREGNANCY = PROHIBITED. Do not use: in adolescents of either sex, men or women who are of childbearing age and not using effective contraception; in pregnant or breastfeeding women.

The French Health Products Agency (ANSM) launched a review of the pregnancy pictograms in 2023; its results had not been made public as of July 2024 (4). Patients' interests would be better served if this review were to culminate in explicit pictograms that genuinely reduce the risk of in-utero exposure, and if the choice were no longer left to drug companies.

QR codes on boxes and patient leaflets: a trend to monitor and, above all, regulate. The boxes and patient leaflets of several products we examined in 2023, in particular those containing *finasteride* or *isotretinoin* (French autorisations), featured a QR code (5,6).

These QR codes direct users to warnings about certain adverse effects, but they must not replace the important information that must be displayed on the box, nor the patient leaflet, printed on paper and supplied in each box, which contains other useful information.

In France, a cross-ministerial trial of electronic patient leaflets for certain drugs was announced for 2024, in which the full patient leaflet would be accessible via a QR code on the box. For drugs used in hospitals, patient leaflets would be replaced by a QR code on the box, providing access to an electronic version of the patient leaflet via a smartphone or tablet, potentially accompanied by interactive forms or videos providing additional practical information. For certain drugs dispensed in community pharmacies, both formats would be provided at first, but the paper format would eventually be phased out and printed at the pharmacy if requested by the patient. The claimed intention of this initiative is to reduce the carbon footprint of drugs, which are estimated to account for 20% of the total emissions generated by France's healthcare sector (7).

However, in view of the difficulty certain patients have in using digital technology, in particular older patients or those who do not have a smartphone with which to access information provided via a QR code, and since internet access is sometimes limited in certain locations, Prescrire considers that it would be irresponsible and dangerous to phase out patient leaflets in paper form, see "Phasing out patient leaflets in paper form: eco-responsible or irresponsible?" p. 199 (8).

Packaging that makes the drug easier to use and safer

In health care, it is a major advantage when a drug's packaging is well suited to the doses required and makes the drug easy and safe to administer. Careful, methodical design of every component of the packaging helps reduce the likelihood of errors.

Fewer manual steps and injections. Several vials are sometimes needed to prepare a single dose, which increases the risk of contamination and manual errors.

A single dose of Ngenla° (somatrogon) often requires several consecutive injections, which is uncomfortable or even painful for the patient, and inconvenient. Previously, the only authorised dose strength of Skyrizi° contained 75 mg of risankizumab, requiring two successive injections to achieve the dose recommended in the SmPC. This product is now available at a dose strength of 150 mg, which is a therapeutic advance because it is now possible to administer the recommended dose in a single injection.

Beware of empty blisters. Certain blister packs include empty blisters, which can confuse patients or the person preparing their drugs regarding the number of doses already taken.

Vydura° (*rimegepant*) is supplied in a blister pack with four blisters: two contain one tablet each, and two are empty. The blister packs of the French product Métopimazine Venipharm° contain eight lyophilisates, but have two empty blisters, although the empty ones are a different shape.

Identifying different dose strengths of the same product. When a product is marketed in several dose strengths, they must be easily distinguishable to reduce the risk of dispensing or administering the wrong one, especially for patients using several dose strengths over the same period.

The boxes of the two dose strengths of Aubagio° (teriflunomide 7 mg and 14 mg) are too similar, differentiated only by blue versus green highlighting of the dose strength.

In contrast, the boxes of the various dose strengths of Buvidal° (buprenorphine) pre-filled syringes are well-differentiated. The products intended for weekly administration are labelled "once weekly" and have a purple stripe, while the ones for monthly administration are marked "once monthly" and have a blue stripe. The various dose strengths are printed in large characters on the box, each highlighted in a different colour.





Buvidal^o (*buprenorphine*) prolonged-release solution for subcutaneous injection in a pre-filled syringe: the once-weekly 24-mg dose strength and the once-monthly 128-mg strength are shown

Identifying the total quantity of drug present.

For injectable drugs, healthcare professionals are less likely to make errors if the dose strength is expressed on the box and label as the total amount of active substance contained within the total volume present in the container, rather than as the quantity per millilitre or as a percentage.

The box and vial label of the two dose strengths of Vegzelma° display the quantity of bevacizumab per millilitre next to the brand name, while the total quantity of bevacizumab in the total volume present in the vial is printed lower down. Failure to give prominence to the total quantity per total volume in the vial increases the risk of calculation errors through confusion and, in turn, wrong-dose errors.

In contrast, the total quantity of *evinacumab* per total volume is very clearly displayed on both the box and vial of Evkeeza°, with coloured highlighting that distinguishes it from the quantity per millilitre.

Harmonisation of the manner in which dose strengths are expressed on products containing the same substance. When different products contain the same active substance, it is safer if their dose strengths are expressed in the same units as this reduces the risk of dose calculation errors, especially when switching between products or from one strength to another.

Consider children by choosing safe, appropriate packaging

When a pharmaceutical product is intended for use in children, its packaging should enable the drug to be administered easily and safely in all the age groups covered by the indication, and it should take into account their ability to swallow in particular. In addition, measures should be taken for all pharmaceutical products to limit access to the substance, to reduce the risk of accidental poisoning.

A paediatric indication = child-appropriate packaging. Symkevi° film-coated tablets (tezacaftor + ivacaftor) are authorised for cystic fibrosis from 6 years of age. According to the patient leaflet, the tablets (which measure 12.7 x 6.8 mm or 15.9 x 8.5 mm) must be swallowed whole, and should not be chewed, crushed or split. They are ill-suited to the treatment of young children who have difficulty swallowing tablets. For each authorised indication, drug companies should market a pharmaceutical form adapted to the age of the population concerned from day one.

Protecting children and other vulnerable populations from accidental ingestion. To prevent accidental poisoning, pharmaceutical products must be inaccessible to children. Child safety features for this purpose had been added to the packaging of some of the drugs we examined in 2023. A childresistant film has finally been added to the blister packs of Lamictalo (lamotrigine) 25 mg to 200 mg tablets (French authorisation). In order to remove a tablet from the pack, a blister must now be detached from the rest of the pack, enabling a corner to be carefully lifted to peel off the outer film, before the tablet can be pushed through the aluminium layer. This system greatly reduces the risk of accidental ingestion and is therefore a real advance.

In line with the recommendations issued in 2019 by the European Pharmacovigilance Risk Assessment Committee (PRAC), the last remaining *methotrexate* tablets on the French market supplied in a multidose bottle (Imetho 10 mg) were withdrawn in late 2023. This is a positive development for the safety of patients and the people around them (9).

Instanyl° (fentanyl) used to be marketed both as a single-dose nasal spray in a child-resistant blister and as a multidose spray in a plastic box with a child-resistant closure. These two presentations have been replaced by Instanyl° DoseGuard°, a multidose nasal spray. It has a child-resistant cap and an unlocking button on the side that must be pushed before a dose can be delivered, thus reducing the risk of delivering multiple doses and of potentially fatal consequences.



Instanyl° DoseGuard° (fentanyl)

In summary: some known flaws persist, but a few tangible improvements have been made.

In 2023, long since identified packaging flaws were still in evidence, while the packaging of other drugs met only the most basic regulatory standards. Nonetheless, the packaging of some products had been improved and made easier or safer to use.

However, packaging still does not seem to be a major concern for certain pharmaceutical companies or health authorities. As a result, reconciling ease of use with safety remains an ongoing challenge in 2024. Yet it is imperative to take into account the needs of patients and health professionals if drugs with high-quality packaging are to be made available to them.

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

> Excerpt from Rev Prescrire July 2024 Volume 44 N° 489 • Pages 538-543

Selected references from Prescrire's literature search

- **1-** Prescrire Editorial Staff "Annual review of drug packaging: choose high-quality packaging for safer health care" *Prescrire Int* 2022; **31** (240): 216-219.
- **2-** Prescrire Editorial Staff "A pictogram on boxes of teratogenic or fetotoxic drugs" *Prescrire Int* 2018; **27** (190): 52-53.
- **3-** ANSM "Questions/réponses à l'attention des titulaires d'AMM, concernant l'apposition du pictogramme "femmes enceintes"" September 2018: 8 pages.
- **4-** ANSM "Le comité scientifique temporaire évaluant l'opportunité de faire évoluer le pictogramme "femmes enceintes" présent sur les boîtes de certains médicaments a ouvert ses travaux" 23 February 2023: 2 pages.
- 5- ANSM "Finastéride 1 mg et chute de cheveux" 6 July 2022: 2 pages.
- **6-** ANSM "Acné sévère et traitement par isotrétinoïne durant la grossesse" 6 July 2023: 3 pages.
- **7-** French Ministry of Labour, Health and Solidarity "Communiqué Planification écologique du système de santé: 2e réunion du comité de pilotage national" 15 December 2023: 3 pages.
- **8-** Prescrire Rédaction "Mieux se comprendre. Difficultés avec le numérique: une entrave à l'accès aux soins" *Rev Prescrire* 2021 ; **41** (450) : 297-298.
- **9-** Prescrire Editorial Staff "Weekly methotrexate: welcome measures to prevent fatal errors" *Prescrire Int* 2020; **29** (216): 154-155.