

Drug packaging, a key factor of quality that sometimes determines the choice of a medicinal product: 2020 review

● *Prescrire* examined the packaging of 190 medicinal products marketed in France in 2020. As in previous years, too few met the standards of quality and safety required of healthcare products. Awareness of certain packaging features is useful in preventing errors and helping patients use their medications properly.

● One important aspect of drug packaging, to ensure that the medicinal product is fully identifiable, is that the international nonproprietary name (INN) of the medicinal substance or substances it contains must be prominently displayed on the various components of its packaging. This identification becomes more difficult when an invented name is chosen, rather than a name incorporating the INN. The packaging, name or composition of a number of old drugs marketed in France was changed in 2020, without seizing the opportunity to make their INNs more visible.

● Some packaging features reduce the risk of errors associated with the pharmaceutical form or dosing frequency, such as the inclusion of dosing devices well suited to the recommended doses, or a warning on the box.

● It is also important to check that the medicinal product has safety devices to protect patients, their families and healthcare professionals, such as a system to prevent needlestick injuries following administration of an injectable drug, or a child-proof cap on multidose bottles.

● It is useful to be familiar with the main features of a medicinal product's packaging when choosing between several products containing the same drug, including those marketed in the same pharmaceutical form. This also helps healthcare professionals prescribe, dispense and administer drugs as safely as possible.

*P*rescrire examined the packaging quality of 190 medicinal products marketed in France in 2020, bringing the total to over 7500 since 1981. Our annual drug packaging review is an opportunity to draw attention to some improvements we observed as well as some persistent flaws. It is also an opportunity to highlight certain specific features, to help healthcare professionals choose

the most appropriate medicinal products and help patients benefit from their efficacy while keeping their dangers to a minimum.

It is still often difficult to identify the composition of medicines

For a medicinal product to be fully identifiable, so that users better understand the product and to reduce the risk of errors, the various packaging items (e.g. box, blister, vial, bottle) must be clearly labelled with the international nonproprietary name (INN) and dose strength of the medicinal substance or substances it contains.

Finding the INN on the box: as difficult as ever due to the prominence given to invented names. One aspect of medication safety is that the medicinal substances a medicine contains must be clearly identifiable. Errors caused by the way in which information is presented on drug packaging are regularly reported to the French Health Products Agency (ANSM). In some cases, patients have taken the wrong medicinal substance entirely, because of the resemblance between the primary packaging (blister packs, vials, bottles, etc.) or boxes of two medicinal products (1).

Yet the invented name was more prominent than the INN on the box and primary packaging in almost half of the packaging analyses *Prescrire* conducted in 2020.

One example is the packaging for Flector° (*diclofenac*) tablets, where the invented name overshadows the INN on the box and blister pack, whereas the INN is clearly visible on the packaging of other products, such as Kipos° (*colecalférol*).

Among the generic drugs marketed under an invented name, this name is very prominently displayed on the packaging of Elfasette° (*desogestrel*), and Lolistrel° and Lolistrel Continu° (*levonorgestrel + ethinylestradiol*), while their INNs are downplayed. This represents a step backwards, since Elfasette° and Lolistrel° were previously marketed under brand names consisting of their INN or INNs followed by the name of the pharmaceutical company, Mylan. It would nevertheless have been possible to make the INNs clearly visible on the packaging, as Pierre Fabre Dermatologie did on the box and blister packs of another generic, Alizem° (*alitretinoin*).

Alizem® Gé
Alitrétinoïne

Alizem® Gé 30 mg
Alitrétinoïne
Capsule molle
PIERRE FABRE DERMATOLOGIE

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The brand name of some medicines was changed, but the INN remained indistinct on the packaging, for example when Normacol° was renamed Normafibe° (*sterculia*).

INNs are still too often indistinct on medicines for non-oral use. Examples include Vablys° (*dequalinium chloride*) and Mycohydralin° (*clotrimazole*) for vaginal use, and Plitican° (*alizapride*) for injection.

The brand names are prominently displayed on the boxes of the suppositories Coquelusédal Nourrissons° and Coquelusédal Enfants° (*soft hydroalcoholic extracts of grindelia and gelsemium*) and Coquelusédal Adultes° (*soft hydroalcoholic extracts of grindelia and gelsemium + niaouli oil*), whereas the name of the substance is more visible on the sides of the box, where the detailed composition is displayed. The blister packs of these suppositories are even less clear, featuring only the target population and brand name, but not the substance.

The eye drops Vizilatan° (*latanoprost*) and Vizitrav° (*travoprost*) have similar brand names and company graphics, creating a risk of confusion between the two products. The boxes could also be stored next to each other in community pharmacies that order drugs alphabetically according to the brand name. The risk of confusion when storing or dispensing these products could be reduced by making their INNs more visible on the packaging (2).

Too many non-unit-dose blister packs allow essential information to be lost. Blister packaging offers a surface with an important role in keeping medicinal products identifiable, especially when removed from the box or when a blister pocket is detached to place doses in a pill organiser. Perforated unit-dose blister packaging is even better, because the information required to identify the drug (the INN, brand name, batch number and expiry date) is present on each blister pocket even after it has been detached from the rest of the blister pack (3).

It is difficult or impossible to identify the contents of detached blister pockets if the information printed on the blister film has not been aligned with the blister pockets in this way. Examples include Alunbrig° (*brigatinib*), Flector° (*diclofenac*) tablets, Lumi-relax° (*methocarbamol*), Prontadol° (*paracetamol + caffeine*), Santuril° (*probenecid*), Slenyto° (*mela-tonin*), Tillhepo° (*ursodeoxycholic acid*) and Twicor° (*rosuvastatin + ezetimibe*). As for Colpermin° (*peppermint oil*), it makes no sense to market a perforated blister pack, covered in information, without aligning it with the perforations!



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Colpermin° (peppermint oil) in perforated blister packs: the printed information is not aligned with the perforations

The way in which information is printed on some blister packs suggests they are unit-dose blisters when in fact they are not: the useful information is not positioned over the blister pockets and therefore does not remain intact when doses are detached. This is the case with Carvecoral° (*ivabradine + carvedilol*), Rinvoq° (*upadacitinib*) and Suvreza° (*ezetimibe + rosuvastatin*).



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Suvreza° (ezetimibe + rosuvastatin): the information printed on the flat surface of the blister pack is not aligned with the blister pockets on the other side

As in previous years, some of the medicinal products we examined in 2020 are marketed in perforated unit-dose blisters packs: Diphante° (*phenytoin*), Forxiga° (*dapagliflozin*) and the box containing 2 capsules of Kipos° (*colecalfiferol*); but these are exceptions.

Fixed-dose combinations: watch out for different strength combinations. A fixed-dose combination is a medicine containing several medicinal substances in the same pharmaceutical form. It is especially easy for patients and healthcare professionals to lose sight of the composition of fixed-dose combinations marketed under an invented

name, as it can mask the fact that they contain several substances. Fixed-dose combinations are sometimes more convenient for patients, reducing the number of dosage units they need to take, provided each substance is of proven clinical value and that the doses chosen are appropriate (4).

Clearly labelling all packaging items with each INN, directly followed by its dose strength, would make these combinations fully identifiable. The coexistence on the market of several combinations can cause confusion between their dose strengths, resulting in errors when prescribing, storing, dispensing, administering or taking them (5).

The boxes of Carvecoral[®] (*carvedilol + ivabradine*), Orkambi[®] (*lumacaftor + ivacaftor*) and Twicor[®] (*rosuvastatin + ezetimibe*) are clearly marked with the dose of each substance, and graphics help distinguish the various strength combinations. In contrast, the blister packs of the various strength combinations of the Carvecoral[®] and Twicor[®] product lines are very hard to tell apart, making errors likely if blister packs become separated from the box. The sachets of the two combinations in the Orkambi[®] product line also look very similar.

The boxes of the different strength combinations of Preminor[®] (*ramipril + amlodipine*) also look alike, and the INN *amlodipine*, printed in pale blue on a white background, is indistinct. The labelling on the blister packs does not align with the blister pockets, and it is difficult to tell the strength combinations apart (6).



Premior[®] (*ramipril + amlodipine*):
resemblance between blister packs increases
the risk of confusion between
the strength combinations (the doses are
reversed: 10 mg + 5 mg, versus 5 mg + 10 mg)

Combining ease of use and safety to reduce the risk of errors

If doses of a medicinal product must be measured accurately or the dosing schedule is unusual (such as weekly administration), it is important that the packaging makes use of the product as safe as possible.

Dosing devices are often unsuitable, causing a risk of dosing errors. The ANSM recommended in 2016 that, for oral liquid medicines

marketed in multidose bottles (our translation), “*the delivery device supplied be graduated in the same units as those used in the summary of product characteristics and the package leaflet to indicate the recommended dose*”. Doses are usually expressed in terms of weight (e.g. milligrams (mg)) in summaries of product characteristics (SPCs) and patient leaflets (7).

The dosing devices supplied with Amglidia[®] (*glibenclamide*, a sulfonylurea antidiabetic), authorised for use in neonatal diabetes, are oral syringes graduated in millilitres (ml), whereas doses are expressed in milligrams in the patient leaflet and SPC. The patient leaflet does not contain a table to help users convert the number of milligrams prescribed per dose into millilitres. Yet two concentrations of this drug have been authorised, one 10 times as concentrated as the other (0.6 mg/ml and 6 mg/ml). Each concentration is marketed in two formats: one in a box containing a syringe with a capacity of 1 ml, and the other in a box containing a 5-ml syringe. All these differences increase the risk of confusion and dosing errors.

Similarly, Epidyolex[®] (*cannabidiol*), authorised for certain severe forms of childhood epilepsy, is marketed in a box containing two types of oral syringes with different capacities. Inaccurate doses are likely to be administered if the larger syringe is used to measure volumes of less than 1 ml. Furthermore, these syringes are graduated in millilitres while the dose is expressed in milligrams in the SPC and, yet again, the patient leaflet lacks a table to help users convert milligrams into millilitres of this 100 mg/ml solution (8).

The oral solution Tussonyl[®] (*oxememazine*) is marketed in a box containing a measuring cup, which is an inaccurate form of dosing device, graduated in 5-ml increments up to 20 ml. The maximum dose of *oxememazine* to be taken at each administration to treat cough in adults and children weighing 20 kg or more is 10 ml; the 15-ml and 20-ml graduations are therefore superfluous. Taking the entire contents of this measuring cup could result in an overdose, increasing the risk of drowsiness and of developing the adverse effects of this sedating antihistamine that also has antimuscarinic and neuroleptic properties (9).

Following reports of errors caused by the fact that *haloperidol* oral solution (Haldol[®] or other brands) was supplied with one of two different dosing devices (an oral syringe or a dropper), Haldol[®] accompanied by an oral syringe was withdrawn from the market. But the decision to keep only the dropper format on the market has not solved the problem of confusion between the number of drops and milligrams, which has also caused dosing errors.

One positive development of this type, identified in 2020, is that the box of Tiapridal[®] (*tiapride*) oral solution, a neuroleptic, now contains a syringe graduated in milligrams, labelled in addition with the INN and the concentration of the solution. This is a real therapeutic advance for a medicinal product previously marketed in a dropper container (6).

Highlighting unusual dosing frequencies. It is important that healthcare professionals and patients are aware if a medicine has an unusual dosing frequency. Specific warnings on its packaging, i.e. the box, the primary packaging (blister pack, a label on a prefilled pen, vial or bottle) and the patient leaflet, help reduce the risk of dosing frequency errors (10).

There is no mention on the box of Prexate° (*methotrexate*), authorised for use in certain autoimmune diseases, that it is to be injected weekly. Yet the European Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the packaging of *methotrexate*-containing products authorised for use as immunosuppressants should state that they are for weekly injection, in order to reduce the risk of daily injections, a potentially fatal error if not detected in time. The European Commission ratified these recommendations in late 2019 (6,10).

In contrast, the glucose-lowering drug Ozempic° (*semaglutide*) is clearly labelled with the statement “une fois par semaine” (once weekly) on the front, two sides and the flap of the box, and on the label on the pen. Fields are also printed on the flap, where the user records their chosen injection day (“jour de la semaine”) and the dates on which their injections were actually performed. All of these measures help ensure that this drug is used correctly (11).



The flap of the box for Ozempic° (*semaglutide*) has fields for recording the day of the week injections will be performed and the actual injection dates

Take care with drugs with a narrow therapeutic index. Marketing oral liquid drugs in single-dose containers eliminates the need to measure doses with a dosing device, or to convert between units if the device is graduated in different units from those used to express the dose in the SPC.

Tsoludose° (*levothyroxine*) oral solution in single-dose containers is an alternative to the many tablets containing this thyroid hormone. However, as the container is opaque (because *levothyroxine* must be protected from light), it is impossible to check whether part of the dose has been left behind, and *levothyroxine* has a narrow therapeutic index. According to the patient leaflet, the entire dose can be considered to have been expelled if the container has been squeezed at least 5 times (12).

Protection from the risk of poisoning and accidental injury

Medication safety is an issue that affects patients, as well as their relatives, caregivers and healthcare professionals. Drugs that can cause poisoning through accidental ingestion or injury when handling them must be packaged in a way that protects everyone involved from these risks.

Bulk bottles: still on the market despite the risk of poisoning. Unlike dry oral forms packaged in perforated unit-dose blisters, tablets and capsules packaged in bulk bottles are not easily identified once placed in a pill organiser.

The contents of a bulk bottle can be accidentally spilled. There is also a greater chance that someone other than the patient, especially a child, could ingest the drug. Even a child-proof cap does not fully prevent this risk. As in previous years, too many drugs were still packaged in bulk bottles in 2020, including some that are dangerous in small quantities. This was the case for a number of cytotoxic drugs we examined: Imeth° 10 mg (*methotrexate*) tablets, Rubraca° (*rucaparib*) and Talzena° (*talazoparib*) (6).

The following drugs were also supplied in bulk bottles: Cernitol° (*pollen extracts*) authorised for benign prostatic hyperplasia; Delstrigo° (*doravirine + lamivudine + tenofovir disoproxil*), Dovato° (*dolutegravir + lamivudine*) and Pifeltro° (*doravirine*), antiretrovirals authorised for the treatment of HIV infection; and the antiepileptics Kigabeq° (*vigabatrin*) and Lamictal° 5 mg (*lamotrigine*). For Lamictal° 5 mg, this was a step backwards, since it was previously marketed in blister packs (6).

Child-proof caps: a simple protective measure, all too often absent. Many of the liquid drugs (mouthwashes or oral liquids) we examined in 2020 were still marketed in bottles lacking a child-proof cap. This was the case for the following mouthwashes containing *chlorhexidine* alone: Chlorhexidine Arrow°, Chlorhexidine Biogaran°, Chlorhexidine Mylan°, Paroex°, Prexidine° and Eludrilperio°. It was also the case for the oral solution Bonasol° (*alendronic acid*) and the syrups Fluisédal° (*promethazine + meglumine benzoate + polysorbate 20*) and Tussisédal° (*promethazine + noscapine*) (6).

Yet adding a child-proof cap is a simple solution for reducing the risks associated with the ingestion of drugs by children (13). The following multidose oral solutions we examined in 2020 did have a child-proof cap: the sulfonylurea antidiabetic Amglidia° (*glibenclamide*); the neuroleptics Epidyolex° (*cannabidiol*), Haldol° (*haloperidol*) and Tiapridal° (*tiapride*); Tussonyl° (*oxememazine*), an antihistamine used for cough; and the strong opioid Zoryon° (*methadone*). In the case of Zoryon°, the box and a label on the bottle even display a warning about the risk of serious and life-threatening adverse effects associated with ingestion of this syrup, especially by a child.

Child-resistant film on blister packs: additional protection, still too rarely used. The use of a child-resistant film on blister packs provides welcome added protection against the risk of accidental ingestion by a child, especially for tablets or capsules that contain particularly dangerous substances.

Unfortunately, the generics Buprenorphine/Naloxone Arrow° and Buprenorphine/Naloxone Mylan° (*buprenorphine + naloxone*) are marketed in blister packs without child-resistant film (6). This is a particularly regrettable choice given that they are generic versions of Suboxone°, which does have this safety feature (14).

Zoryon° capsules (*methadone*) are supplied in blister packs with a child-resistant film, a welcome choice given the risk of serious and potentially fatal adverse effects if ingested by a child, a risk that is mentioned on the boxes and blister packs.

A needle protection system very often present to prevent accidental injuries after injections. Many injectable medicinal products are equipped with a system to protect the needle after injections, in order to protect patients, caregivers and healthcare professionals from needlestick injuries. This is the case for Dupixent° (*dupilumab*), Fasentra° (*benralizumab*) and Pelgraz° (*pegfilgrastim*), supplied in pre-filled syringes and pens, and for Fulphila° (*pegfilgrastim*), Inhixa° (*enoxaparin*), Skyrizi° (*risankizumab*) and Tegsedi° (*inotersen*) in pre-filled syringes.

In contrast, Waylivra° (*volanesorsen*), supplied in pre-filled syringes, has no such system.

In summary Packaging quality sometimes determines the choice and sometimes makes a product unsafe

Knowledge about drug packaging is useful in various ways. It enables doctors to prescribe the product with the best-quality packaging rather than other products containing the same substance. When dispensing drugs, it enables pharmacists to help patients use their medications properly; this may even include opening the box in front of the patient. It also enables healthcare professionals to administer drugs safely.

As in previous years, INNs were still too often overshadowed by the invented name on packaging in 2020. And only a handful of the medicines marketed in dry oral forms examined by *Prescrire* in 2020 were supplied in perforated unit-dose blisters.

Worse yet, many drugs that are toxic in the event of accidental ingestion, especially by a child, were marketed in bulk bottles or blister packs with no child-resistant film. And many liquid medicines packaged in bottles without a child-proof cap remain on the market.

A few advances in safety are to be commended, such as clearly displayed warnings for patients about unusual dosing frequencies, and the almost sys-

tematic presence of a needle protection system to prevent needlestick injuries after injections.

The ANSM's 2018 recommendations on drug labelling offer hope that INNs will be displayed more clearly, at least on drugs authorised by the ANSM through a French national marketing authorisation procedure (1). Pharmaceutical companies that develop and manufacture drugs, and the agencies that authorise them, still have a long way to go in protecting patients and their families from dangerous drug packaging.

**Review produced collectively
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