2019 Prescrire Packaging Awards

When *Prescrire* evaluates a drug's harm-benefit balance, the quality of its packaging is one of the factors examined. We answer several questions during our packaging examinations. Does the packaging ensure that the drug is easily and accurately used, does it ensure the safety of patients and their family and carers? Conversely, are any aspects of the packaging dangerous, or does it lack anything necessary for the safe use of the drug?

Our packaging examinations take account of many factors: the clinical situation in which the drug will be used; the patients liable to receive it, especially pregnant women, children or elderly patients; whether family members, carers or a nurse will prepare and administer it; and whether it will be used in an emergency, hospital or community setting, obtained on prescription, on the advice of a community pharmacist, or bought by the patient from an internet retailer.

Every aspect of the packaging is assessed for quality and user safety. We examine in particular: whether international nonproprietary names (INNs) are clearly legible and whether different dose strengths of the same drug are easily distinguishable; the clarity of any information presented graphically, such as diagrams, dosing schedules, symbols or pictograms; the devices for preparing, measuring and administering doses; the risk that children will be able to ingest the drug unnoticed by their carers; and the quality and clarity of the information provided in the patient leaflet on how to use the product, its adverse effects, and the situations and patient groups in which the drug poses a particular risk.

The 2019 Packaging Awards pertain to the packaging of drugs evaluated in our French edition in 2019.

2019 PACKAGING AWARD

Isentress° granules for oral suspension (***raltegravir***) MSD (Rev Prescrire n° 431)

For the clear, informative "*instructions for use*" booklet inside the box of the paediatric form of this antiretroviral drug, now authorised for use in neonates. This booklet, provided in addition to the patient leaflet, contains a wealth of useful information to help prevent errors and the dangers posed by the extemporaneous preparation of this drug, including a precise description of the items required for its preparation (all of which are supplied in the box), and each preparation step. Various procedures are illustrated, such as how to read the graduations on the syringe correctly, how to administer the preparation, and how to clean all the equipment after use.

The lower excipient content of reconstituted powders is an advantage over ready-to-use oral preparations, because some excipients, such as propylene glycol, ethanol and castor oil, can have serious adverse effects in children. But their reconstitution is often complex and rarely adequately explained in the patient leaflet. This booklet is an example of what ought to be the rule, due to the effort invested in providing unambiguous, easy-to-follow instructions.

RED CARDS

Packaging for children: savings at the expense of safety

Firazyr° solution for subcutaneous injection (***icatibant***) Shire (Rev Prescrire n° 423)

For not marketing a paediatric version of this drug, initially authorised for adults with a rare genetic disorder, when it was subsequently authorised for use in children from the age of 2 years. Adults receive the same dose at each injection, justifying the fact that the syringe supplied has no graduations. The syringe has not been adapted for use in children, even though paediatric doses are based on body weight. The solution chosen by the pharmaceutical company and drug regulatory agencies is to give parents a separate box, containing a graduated syringe and a device to connect the two syringes to transfer the contents of the non-graduated syringe into the graduated one. This unnecessarily complicated solution is likely to cause errors.

Inovelon° oral suspension (***rufinamide***) Eisai (Rev Prescrire n° 429)

For not adapting the dosing device supplied in the box when the product's indications were extended to include infants. Infants require lower doses of this antiepileptic than adults and children from 4 years of age. The syringe capacity (20 ml) remains unchanged but is far higher than necessary for measuring infant doses (e.g. 1.25 ml for an infant weighing 10 kg), making overdoses likely.

Phosphoneuros° oral solution (***phosphorus***) Bouchara Recordati (Rev Prescrire n° 428)

For insufficient improvements to packaging that has caused fatal overdoses of this medicine used in neonatology. The smallest volume that can be measured with the dosing device is 5 drops, precluding accurate measurement of the lower doses required for children weighing less than 5 kg. The patient leaflet makes no mention of this lower limit and offers no advice on how to prepare smaller doses. It also lacks a table to enable users to convert the number of milligrams of *phosphorus* prescribed to the number of drops to measure out. There are no detailed explanations or illustrations of how to prepare and administer the drug.

Rotarix° oral suspension (***rotavirus vaccine***) GlaxoSmith-Kline (Rev Prescrire n° 432)

For the strong resemblance of the administration device provided in France with this oral vaccine to a syringe for injection, which has resulted in wrong-route errors, whereas Rotarix° is authorised in the European Union in a different container that does not resemble a syringe.

Siklos° 100 mg and 1000 mg scored tablets (***hydroxycarbamide***) Addmedica (Rev Prescrire n° 431)

For not improving the labelling so that the two dose strengths of this cytotoxic drug are easier to distinguish, to mitigate the risk of confusing one for the other. Overdoses have occurred in children as a result of dispensing and administration errors, provoking serious haematological disorders. Furthermore, it is dangerous to supply cytotoxic drugs as loose tablets in a bulk bottle. The person preparing the tablets is at higher risk of exposure to the drug and, in the hospital setting, the tablets must be repackaged and relabelled, creating an additional step at which wrong-strength errors can occur.

RED CARDS

Insufficient efforts to prevent ingestion by children

Alfa-Amylase Biogaran Conseil° (**a**) Biogaran and **Maxilase Maux de Gorge°** (**a**) Sanofi Aventis syrups (***alpha-amylase***) (Rev Prescrire n° 426); **Clarix Toux Sèche Adultes°** (**a**), **Clarix Toux Sèche Enfants°** Cooper, and **Vicks Sirop Pectoral°** (**a**) Procter & Gamble Pharmaceuticals syrups (***pentoxyverine***) (Prescrire Int n° 208); **Dolko°** (**b**) oral solution (***paracetamol***) Thérabel Lucien Pharma (Rev Prescrire n° 434); **Nausicalm°** syrup (***dimenhydrinate***) Nogues (Rev Prescrire n° 423) (**c**); **Phénergan°** (**d**) syrup (***promethazine***) DB Pharma (Rev Prescrire n° 424); **Phosphoneuros°** oral solution (***phosphorus***) Bouchara Recordati (Rev Prescrire n° 428); **Potassium Liberty Pharma°** (**e**) syrup (***potassium***) H2 Pharma (Rev Prescrire n° 426).

For the absence of a child-proof cap on the bottles of these 10 products, especially when child-proof caps are present on so many other medicines in bottles. The caps on these 10 medicines do not sufficiently protect children. They give children easy access to the contents of the bottle, placing them at risk of the adverse effects of the substances they contain.

Umbrella brands that give insufficient prominence to INNs and dose strengths

Actifed LP Rhinite Allergique° (**d**) tablets (***cetirizine + pseudoephedrine***), **Actifed Rhume°** tablets (***paracetamol + pseudoephedrine + triprolidine***), **Actifed Rhume Jour et Nuit°** tablets (***paracetamol + pseudoephedrine*** or ***paracetamol + diphenhydramine***) Johnson & Johnson Santé Beauté; **Dolirhume°** tablets (***paracetamol + pseudoephedrine***), **Dolirhumepro°** tablets (***paracetamol + pseudoephedrine*** or ***paracetamol + doxylamine***) Sanofi Aventis; **Humex Rhume°** tablets and hard capsules (***paracetamol + pseudoephedrine*** or ***paracetamol + chlorphenamine***) Urgo Healthcare; **Nurofen Rhume°**, **Rhinureflex°** tablets (***ibuprofen + pseudoephedrine***) Reckitt Benckiser Healthcare; **Rhinadvil Rhume°** tablets, **Rhinadvilcaps Rhume°** soft capsules (***ibuprofen + pseudoephedrine***) Pfizer Santé Familiale; **Rhumagrip°** tablets (***paracetamol + pseudoephedrine***) Cooper (Rev Prescrire n° 424).

For packaging that gives too little prominence to the international nonproprietary names (INNs) and dose strengths of the drugs these products contain. It makes it difficult to identify the presence of the sympathomimetic vasoconstrictor *pseudoephedrine*, which can provoke cardiovascular events and ischaemic colitis. It also makes it difficult to identify the presence and quantity of *paracetamol*, an overdose of which can damage the liver. All but Rhumagrip° belong to umbrella brands, the principle of which is to sell a variety of medicines, containing different active substances, under the same brand name.

The French Health Products Agency (ANSM) has recommended ending the use of umbrella brands, due to the risk of confusion between products of the same brand and the dangers they pose to patients.

Psychotropic oral suspension with a confusing, inaccurate dosing device

Deroxat° oral suspension (***paroxetine***) GlaxoSmithKline (Rev Prescrire n° 423).

For the confusing measuring cup provided with this antidepressant, graduated in both milligrams and millilitres, which has already caused dosing errors. Even without this flaw, a measuring cup is not an accurate dosing device.

Patient leaflets that understate the harms

Ellaone° tablet (***ulipristal***) HRA Pharma (Prescrire Int n° 212).

For the insufficient information in the patient leaflet on the risk that using hormonal contraception within 5 days of taking *ulipristal* will reduce the efficacy of *ulipristal*. It has been known since 2015 that administration of hormonal contraception during this 5-day period increases the likelihood of ovulation, which could result in an unintended pregnancy.

Entalgine° cutaneous gel (***diclofenac***) Cooper (Rev Prescrire n° 434); **Flurbiprofène Sandoz Conseil°** (**d**) Sandoz, **Strefen°**, **Strefen Sans Sucre°** lozenges (***flurbiprofen***) Reckitt Benckiser Healthcare (Prescrire Int n° 202); **Rhinadvil Rhume°** tablets (***ibuprofen + pseudoephedrine***) Pfizer Santé Familiale (Rev Prescrire n° 424); **Ipraféine°** tablets (***ibuprofen + caffeine***) Sanofi Aventis (Rev Prescrire n° 426).

For the insufficient information in the patient leaflets on the potential harms of taking nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy. These patient leaflets do not mention the increased risk of spontaneous abortion or concerns over the risk of malformations when NSAIDs are taken during the first trimester of pregnancy, or the risk of potentially irreversible renal damage or pulmonary arterial hypertension in the unborn child when taken in the second trimester. They only state that the product is contraindicated from the sixth or seventh month of pregnancy.

NSAIDs should be avoided throughout pregnancy, because there is no evidence that contraindicating their use from the sixth month of pregnancy is sufficient to avoid harming the unborn child.

a- *In addition, the packaging of these multidose oral liquids lacks a dosing device.*
b- *In addition, the INN paracetamol and its dose strength are difficult to see.*
c- *Addition of a child-proof cap was authorised in 2018. It was still absent however from a batch purchased from a wholesale distributor on 2 January 2020, due to expire in November 2021.*
d- *The pharmaceutical companies concerned no longer market these products in France. We left them on this list in case any pharmacies still have them in stock.*
e- *In response to our request, H2 Pharma informed us that plans are underway to add a child-proof cap to the bottle. This company markets another multidose potassium syrup (Potassium H2 Pharma°) that acquired a child-proof cap in 2019, as well as a dosing device, in the form of a measuring cup with 5 ml and 15 ml graduations.*