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° 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°; *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° 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° and Doliprane°) 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° 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° 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.*

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

3- Afssaps "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°". In: "Medic'am 2004-2009" juin 2010 (ameli.fr): extraction papier 1 page.

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