

## Who benefits from the European Paediatric Regulation?

Response to the European Commission's public consultation  
on the lessons learnt from the first 5 years of application of the Paediatric Regulation (1)

### Summary:

- The aim of the Paediatric Regulation (European Regulation (EC) No 1901/2006, adopted in 2006) was to encourage the development of medicinal products suitable for children. However, the regulation was constructed less around children's needs than on incentives for pharmaceutical companies.
- *Prescrire* has chosen to respond to the consultation on the lessons learnt from the first 5 years of the European Paediatric Regulation by detailing one example in France that illustrates particularly well some of the most lamentable aspects of the application of this regulation: Cozaar<sup>o</sup> oral suspension, the paediatric form of the antihypertensive drug *losartan*.
- The packaging of Cozaar<sup>o</sup> oral suspension is poorly designed and dangerous. Furthermore, the drug is difficult to obtain from retail pharmacies via wholesalers, and the pharmaceutical company MSD France chose not to request its inclusion on France's list of reimbursable drugs. Cozaar<sup>o</sup> oral suspension also highlights the failure of the Paediatric Regulation to stimulate the development of the medicines most useful for children.
- Yet MSD France has been granted a 6-month extension to its market exclusivity on *losartan* in France, even for its non-paediatric indications. In the case of Cozaar<sup>o</sup> oral suspension, the application of the Paediatric Regulation has resulted in higher health spending in France than if a generic had been used, in order to reward a pharmaceutical company for marketing a paediatric medicinal product that is unsuitably packaged, difficult to obtain, not reimbursable, and not the standard treatment for children with hypertension.
- The results of the other reward scheme established by the Paediatric Regulation — paediatric-use marketing authorisation (PUMA) — are no more encouraging. PUMAs incentivise companies to develop a product exclusively for paediatric use based on a drug whose patent protection has expired, by making the holder eligible for a 10-year market monopoly and possibilities of exemption from certain fees. However, in the five years since the Paediatric Regulation came into force, the PUMA process has provided very little benefits to children: only one PUMA has been granted, and for a medicinal product that France's National Authority for Health rated as representing only a minor therapeutic advance over existing therapies.
- As of 2012, the tangible results of the Paediatric Regulation are disappointing. The regulation mainly benefits the pharmaceutical industry and benefit children's health hardly at all. Its implementation must change profoundly to:
  - provide real therapeutic progress for children;
  - reduce the dangers to which children are exposed due to the prevalence of poorly designed packaging.

# Who benefits from the European Paediatric Regulation?

## Response to the European Commission's public consultation on the lessons learnt from the first 5 years of application of the Paediatric Regulation (1)

The stated aim of the Paediatric Regulation (European Regulation (EC) No 1901/2006, adopted in 2006) is "to improve the health of children in Europe" by encouraging the development of medicines for use in children of all age groups (2). However, the regulation focuses less on children's needs (1) than on incentives for pharmaceutical companies (2) (3).

In September 2012, the European Commission launched a public consultation to learn lessons from the first 5 years of application of the Paediatric Regulation (1). The comments in the Commission's consultation document corroborate the conclusions of the reports prepared by the European Medicines Agency (4,5).

*Prescrire* agrees with the European Medicines Agency that the application of the Paediatric Regulation has been extremely disappointing. In France, one case exemplifies the most appalling aspects of these last 5 years of the Paediatric Regulation: the oral suspension form of the antihypertensive paediatric medicine Cozaar<sup>®</sup> (6). Rather than responding to each item in the consultation document, *Prescrire* has chosen to detail this particularly instructive example.

### Cozaar<sup>®</sup> oral suspension: deplorable

The paediatric form of the angiotensin II receptor antagonist *losartan* – Cozaar<sup>®</sup> oral suspension – was the first paediatric drug in France to be granted a 6-month extension to its supplementary protection certificate, also covering its non-paediatric indications. This is one of the two main ways the Paediatric Regulation rewards pharmaceutical companies for developing paediatric medicines.

**Cozaar<sup>®</sup> oral suspension: unsuitable, dangerous packaging, and difficult to obtain.** *Losartan* – Cozaar<sup>®</sup> oral suspension was marketed in an inadequate pharmaceutical form, since it requires reconstitution before use, and in unsuitable, complicated packaging that is dangerous because it has a

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1- The "lists of paediatric needs" drawn up by the Paediatric Committee have become an inventory of existing practices (drugs indicated for use in adults and off-label used in children, or that have paediatric marketing authorisation in some countries), but some of these practices are not evidence-based or may even be harmful. And some needs are not covered (ref. 2).

2- There are two main ways of obtaining rewards:

- for new drugs or MA variations for drugs that are still under patent protection, in return for supplying study results considered in line with the paediatric investigation plan previously approved by the European Medicines Agency, it is possible to obtain a 6-month extension of the supplementary protection certificate of the medicine, even for the medicine's non-paediatric indications; this is the reward that the company that markets Cozaar<sup>®</sup> oral suspension obtained in France;

- for drugs that are already marketed but no longer protected by a patent or a supplementary protection certificate, if marketing authorisation is obtained exclusively for use in children, this paediatric-use marketing authorisation (PUMA) protects the data utilised to obtain the authorisation for a 10-year period, which basically means a 10-year market monopoly for the pharmaceutical company (ref. 3).

The economic incentives provided by the Paediatric Regulation for companies that develop paediatric drugs bear no relation to the real therapeutic needs of children or the true costs of the research conducted (ref. 3).

number of flaws liable to cause confusion and dosing errors. *Prescrire's* Packaging Working Group analysed its packaging and identified the following shortcomings:

- The suspension is not ready to use, and the materials provided for its reconstitution and administration are conducive to error:
  - The pack contains 473 ml of solvent whereas only 200 ml is required; the capacity of the bottle provided for the reconstituted suspension is 40 ml greater than required, creating the risk of adding too much solvent and administering a drug that is too dilute;
  - This bottle is not labelled “shake before use”, yet shaking is essential to produce a uniform suspension;
- The oral dosing syringe provided is graduated in millilitres, and calculations to convert the milligrams prescribed into the equivalent volume to measure are a potential source of error (6,7).

We also noted that, although this antihypertensive drug is intended for chronic use outside the hospital setting, it was difficult to obtain in France (7). Finally, the company chose not to ask for Cozaar<sup>®</sup> oral suspension to be included on the list of reimbursable drugs, requiring patients to pay the whole retail price of close to a hundred euros themselves.

Yet in spite of all these shortcomings, MSD France, the pharmaceutical company that markets this medicinal product, has been granted a 6-month extension to its market exclusivity for *losartan* in France: a highly profitable arrangement for the company but not for the public purse (3).

**The regulation does not encourage development of the medicines most useful for children.** For children with hypertension, when antihypertensive medication is considered necessary, the preferred drugs are thiazide diuretics and beta-blockers (8). In adults, drugs belonging to the angiotensin converting enzyme (ACE) inhibitor class are better established than those of the angiotensin II receptor blocker class. No ACE inhibitors indicated for children have been made available in France in a paediatric form, yet the ACE inhibitor class includes some better established drugs than *losartan* (8,9).

The European Paediatric Regulation does not encourage development of the drugs most useful for children, which are often old drugs no longer protected by a supplementary protection certificate. Drugs no longer covered by a supplementary protection certificate are governed by Article 45 of the Paediatric Regulation and no incentives, such as a market exclusivity extension, are offered to companies for marketing a paediatric form (4,5).

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3- According to figures from the French national health insurance fund for salaried workers (Cnamts) on reimbursement requests in France during 2009, reimbursements for *losartan* (excluding the *losartan* + hydrochlorothiazide combination) over a 6-month period totalled 27 million euros (ref. 14).

4- Article 45 allows the Paediatric Committee to reassess old drugs that are no longer protected by a supplementary protection certificate. These reassessments are mainly used to clarify the paediatric information in the various national summaries of product characteristics, e.g. to add paediatric dosages or a statement that no data are available in children, as appropriate. One Article 45 assessment led to restrictions on the use of oral metoclopramide in children. Forty or fifty drugs undergo reassessment under Article 45 per year (ref. 16). Unfortunately, health authorities do not use these reassessments to request improvements to the packaging of drugs with paediatric indications, to better adapt them to use in children.

5- US regulations allow the FDA to demand clinical trials on certain drugs (even going so far as to specify the design of the trial), based on a list of needs and priorities drawn up by the FDA and the National Institute of Health (NIH). This provision was added following the observation that pharmaceutical companies do not spontaneously focus their paediatric R&D efforts on the priority needs of children (ref. 17).

**In summary.** In France, the application of the Paediatric Regulation has resulted in higher health spending than if generics had been used earlier, in order to reward a pharmaceutical company for marketing a paediatric medicinal product that is unsuitably packaged, difficult to obtain, and not the standard treatment for children with hypertension.

## **Paediatric-use marketing authorisation (PUMA): very few results**

The European Paediatric Regulation also established a scheme to encourage companies to develop medicines reserved exclusively for paediatric use based on medicines whose patent protection has expired: paediatric-use marketing authorisations (PUMA) (2,3,10).

PUMA makes the company eligible for a 10-year market monopoly and exemption from certain fees (3).

In the five years since the Paediatric Regulation came into force, the PUMA process has provided very little benefit to children.

One PUMA was requested for an influenza vaccine containing the adjuvant MF59C.1 (Fluad<sup>o</sup>) for use in children from 6 months to less than 9 years of age. The recommendation of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) was that the vaccine's negative harm-benefit balance precluded approval of this PUMA (11).

The only PUMA to have been granted by the European Commission was for a *midazolam* oromucosal solution (Buccolam<sup>o</sup>) for the "treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to less than 18 years)" (12). France's pharmacoeconomic committee (Commission de la Transparence), part of the "National Authority for Health" (Haute autorité de santé, HAS), rated it as representing only a minor therapeutic advance over existing therapies (ASMR IV) (13).

## **Stronger implementation of Paediatric Regulation is needed**

As of 2012, the tangible results of the Paediatric Regulation are disappointing. It is better to tell the children of the European Union, their parents and their care providers the truth: the current Paediatric Regulation mainly benefits pharmaceutical companies and benefits children's' health hardly at all. Its implementation must change profoundly to provide real therapeutic progress for children.

The Paediatric Committee (PDCO) of the European Medicines Agency has a key role in ensuring that the regulation meets children's therapeutic needs.

The Paediatric Committee must:

- Ensure that children's priority therapeutic needs are met, by re-focusing lists on unmet needs rather than producing inventories of existing practices, particularly when these practices are harmful to children;
- Ensure that medicines with paediatric indications actually represent a tangible therapeutic advance, according to the definition of significant therapeutic benefit established by the European Commission when it implemented the regulation (15);
- Put pressure on the Coordination Group (CMDh) charged with assessing the paediatric data on old medicines, in accordance with the worksharing procedure laid down in Article 45, so that these assessments deliver practical improvements (paediatric packaging and forms).

**European children are entitled to benefit from research that best matches their real therapeutic needs and from medicinal products whose therapeutic benefit is properly evaluated, by comparison with existing products.**



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