

Information given in summary of product characteristics of drugs prescribed to children in the community in the Netherlands

Category	Example	No (%) of summaries (n=1421)	No (%) of prescriptions (n=56 731)
Child mentioned with indication of age	Children 2-5 years: 10 mg per day	653 (46.0)	32 180 (56.7)
Child not mentioned	Only "patients" in general mentioned	302 (21.3)	11 688 (20.6)
Child mentioned without indication of age	Children: 0.75 mg/kg in twice daily	280 (19.7)	11 108 (19.6)
Child mentioned but advised against use for all ages	Should not be used in children; safety and efficacy have not been established in children	140 (1.0)	1 328 (2.3)
Child mentioned and age estimated on basis of description	Adults and older children: 10 mg per day	19 (1.3)	219 (0.4)
Child mentioned and age estimated on basis of weight	Children >30 kg: 10 mg per day	13 (0.9)	130 (0.2)
Summary of product characteristics not available		14 (1.0)	78 (0.1)

scriptions and were mainly dermatological and liquid preparations.

The table shows the official labelling of drugs prescribed for children. In 21.3% of the prescriptions for licensed drugs, use in children was not mentioned in the summary, and 19.7% mentioned use in children but without any indication of age. Although the summaries of remaining drugs indicated age, children were often divided into just two age groups.

Overall, 22.7% (15 453) of the prescriptions for children were used off label. Drug groups with the highest percentages of off label use were urologicals or sex hormones (mainly oral contraceptives; 85.9%), ophthalmological and otological drugs (79.4%), dermatological drugs (55.9%), and cardiovascular drugs (48.3%). In the group with the highest number of prescriptions—respiratory drugs—16.1% of all prescriptions were used off label.

## Comment

Many licensed drugs used by children in the community are poorly labelled for use in children, resulting in high

percentages of off label use. Therefore labelling for children needs to be improved, with the support of everyone working in pharmacotherapy.

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# Unlicensed and off label prescription of drugs to children: population based cohort study

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Drugs are subject to licensing procedures to ensure their quality, efficacy, and safety, but many drugs used to treat children in hospital are either not licensed for use in children ("unlicensed") or are prescribed outside the terms of the product licence ("off label").<sup>1</sup> Little is known about such prescribing in general practice, so we conducted a cohort study in primary care in the Netherlands to investigate the subject.

## Methods and results

We retrieved data from the integrated primary care information project, a longitudinal observational database containing information from computer based patient records of 150 general practitioners in the Netherlands. The system complies with European Union guidelines on the use of medical data for medi-

cal research and has been proved valid for pharmacoepidemiological research.<sup>2</sup>

Within the dynamic population of children (0-16 years) registered in 1998, we conducted a one year population based cohort study. From a source population of 53 702 eligible children, we randomly sampled 25% (n=13 426; 6941 (51.7%) boys), which formed our final study population. During the year 8271 (61.6%) children consulted their general practitioner at least once; the median was one consultation a year. We classified all 17 453 drug prescriptions issued to 6141 (45.7%) children according to the licensing status of the drug,<sup>1</sup> by reference to the official product licence, as provided by the Dutch Medicines Evaluation Board.

Seventy one per cent (12 405) of prescriptions were for drugs licensed for use in children and prescribed in agreement with the product licence. Of the remaining 5048 (28.9%) prescriptions, 2667 (15.3%, 95% confi-

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Classification of drugs prescribed to children in primary care

Category	No (%) (n=17 453)
Licensed for use in children	12 405 (71.1)
Off label* for:	
Age	699 (4.0)
Dose	978 (5.6)
Frequency	279 (1.6)
Indication	565 (3.2)
Dosage form	190 (1.1)
Route of administration	4 (<0.1)
Total off label prescriptions	2 381 (13.6)
Unlicensed for use in children:	
No information in product licence on use in children†	1 453 (8.3)
Contraindicated in children	152 (0.9)
Modified preparation‡	1 062 (6.1)
New drugs	0
Total prescriptions for drugs unlicensed in children	2 667 (15.3)

\*As drugs in off label category can be classified under more than one group, totals add up to more than 2381 prescriptions.  
 †No information on use in children found in any subsection of product licence.  
 ‡Drugs produced under a special manufacturing licence—have not been subject to licensing regulations and therefore have no product licence.

dence interval 14.8% to 15.8%) were for drugs not licensed for use in children and 2381 (13.6%, 13.1% to 14.2%) were off label prescriptions for licensed drugs (table). The drugs most often prescribed unlicensed or off label were fusidic acid (ophthalmological gel), salbutamol (aerosol), deproprine citrate, amoxicillin, and fluticasone (aerosol). The baseline risk of receiving one or more unlicensed or off label prescription was 45.5% (44.3% to 46.8%) for children who received at least one prescription during the study period. The risk was 18% (10% to 26%) higher for girls than for boys. Compared with children aged 6-12 years, the relative risk of receiving unlicensed or off label prescriptions was 2.6 (2.4 to 2.9) in children aged 6-24 months and 1.7 (1.6 to 1.9) in children aged 2-6 years. The overall risk of receiving an unlicensed or off label prescription was 13.9% (13.5% to 14.3%) per consultation.

Comment

The absolute risk of prescription of unlicensed and off label drugs in children was substantial in this Dutch general practice setting. The risk is lower than

in secondary and tertiary care,<sup>1</sup> but the potential negative health impact of these findings should be considered. Although unlicensed and off label prescribed drugs do not necessarily carry an actual threat to the health of a child, the risk of adverse drug reactions is high, as adequate dosing schemes have often not been assessed.<sup>3</sup> For instance, bone demineralisation and impairment of growth may follow long term use of respiratory corticosteroids in children.<sup>4</sup> Similarly, the use of highly dosed deproprine citrate in small children can cause hallucinations, agitation, ataxia, and anxiety.<sup>5</sup>

A considerable number of drugs prescribed to children in general practice are not licensed for use in children or are prescribed off label. Unlicensed and off label prescription of drugs in general practice is less frequent than in a clinical care setting but is still substantial, especially as the absolute number of children using such drugs is much higher than in secondary and tertiary care. This situation is highly unsatisfactory, and efforts should be made to improve it.

Contributors: GW\*tJ contributed to the design, assessed the prescriptions for unlicensed and off label use, and conducted the statistical analyses. IAE contributed to the design and prepared the data for assessment. BHChS and JNvdA had the original idea for the study. MCJMS coordinated access to the IPCI database and contributed to the statistical analysis. GW\*tJ wrote the paper, and all other authors were involved in editing the manuscript. BHChS is the guarantor.

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A medical mishap  
 Caustic eye drops



A patient attending for day case cataract surgery had phenol drops instilled into the right eye instead of bupivacaine local anaesthetic. Although bupivacaine is the only eye drop used in the day case centre in this type of bottle, phenol is used topically by chiropractors. The similarity of the bottles highlights the importance of reading a label before administration of a treatment. This mishap also shows the need for cross specialty risk management when different departments use the same work space. The caustic burn was treated successfully, and the patient eventually achieved good vision after uncomplicated cataract surgery.

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We welcome articles of up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.