Eur J Clin Pharmacol (2012) 68:21–28
DOI 10.1007/s00228-011-1097-1

REVIEW ARTICLE

Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature

Jennifer Mason · Munir Pirmohamed · Tony Nunn

Received: 20 April 2011 / Accepted: 29 June 2011 / Published online: 22 July 2011

Abstract The use of unlicensed and off-label medicines in children is common because trials in children have not usually been performed during the drug development process. Consequently, the information available to paediatricians may not always be as detailed or as robust as that available when prescribing a medicine that is licensed for an approved indication. This has led to concerns that children may be receiving drugs at dosages that either lack efficacy or present safety problems. The latter in particular has received a great deal of attention. In this narrative review, we have evaluated the use of off-label and unlicensed medicines in children and whether and how frequently this predisposes to adverse drug reactions.

Keywords Drug toxicity · Drug eruptions · Adverse drug reaction reporting systems · Drug labeling

Introduction

In adults, the risk factors for adverse drug reactions (ADRs) have been defined as old age, polypharmacy and complex underlying disease, but in children, the risk factors (other than polypharmacy) are poorly understood [1, 2]. A factor that has received some attention in this population is the use of off-label and unlicensed medicines [3]. The necessity of using off-label and unlicensed medicines in children is a consequence of how, historically, medicines have been developed and regulated.

The regulation of medicines

Before a new medicine can be approved for use by patients, the manufacturer needs to submit specified information on its quality, safety and efficacy to the relevant national medicines regulatory body. If the new medicine is approved, it is authorised and issued with a Marketing Authorisation (MA). The summary of product characteristics (SmPC) is the important document that is the result of the whole process. It provides vital information for the prescriber that includes the precise indication and dosage of the product, instructions for administration, contraindications, interactions and possible adverse effects. A condition of the approval is that the medicine is only marketed for use under the terms outlined in the MA since these terms reflect the content of the original information submitted by the manufacturer. However, this does not preclude the use of the medicine outside the terms of the MA by individual clinicians.

Off-label and unlicensed medicines

If a medicine has an MA, but is prescribed and/or administered outside the terms of that MA, this is referred to as *off-label use* or *unlicensed use*; we use the term off-label in this article. If a medicine does not have approval in the country in which it is prescribed and/or administered, it is referred to as an *unlicensed medicine*. It is important to note, however, that the exact definitions vary between authors.

J. Mason (✉) · T. Nunn
Alder Hey Children's NHS Foundation Trust,
Eaton Road,
Liverpool L12 2AP, UK
e-mail: jennifer.mason@alderhey.nhs.uk

M. Pirmohamed
Department of Molecular and Clinical Pharmacology,
Institute of Translational Medicine, University of Liverpool,
Wolfson Centre for Personalised Medicine Brownlow Street,
Liverpool L69 3GL, UK

Off-label and unlicensed medicine use in paediatrics

Changes to the way medicines are developed mean that every new medicine under development in Europe must have a paediatric investigation plan (PIP) [4], these changes, which were introduced in 2007, are likely to take time to work through into paediatric practice. In the meantime, the use of off-label and unlicensed medicines remains common in this context. A review of studies of off-label and unlicensed medicine prescribing in children showed that it ranged from 3.3 to 56% of prescriptions in community practice, and 36 to 100% in hospital settings [1].

This clearly has implications for the prediction, avoidance, detection, and treatment of ADRs. Safety data for an approved medicine that is being used off-label may not always be relevant or applicable because it relates only to the use of the medicine as specified by the manufacturer. Unlicensed medicines may also not have any safety data detailed in an MA.

Off-label and unlicensed medicine use and ADRs

The results of studies that have examined the association between ADRs and medicines used in this way show much variation. The reasons for this include differences in study design and definitions used. As preparation for a prospective study of ADRs and off-label and unlicensed medicines in children [5], we undertook a comprehensive literature search to evaluate how other investigators have approached the study of off-label and unlicensed medicines. We provide a narrative review of their methodologies and results, and discuss the issues relevant to their interpretation.

Materials and methods

A Medline search of titles and abstracts from 1950 to the present was performed using the search terms unlicensed/off-label/license/licensed/licensing/label/labelled/labelling/approved/approval/unapproved/prescription/prescribed/prescribing/prescribe/prescriber(s)/incorrect AND adverse effects/adverse drug reaction reporting systems/drug therapy/pharmaceutical preparations AND child/child, preschool. An EMBASE search of titles and abstracts from 1980 to the present was also performed using the search terms unlicensed and off-label use AND child AND adverse drug reaction/drug surveillance program. The limits Human and English Language were applied to both searches.

The method used to select papers for inclusion is summarised in Fig. 1, and this was carried out by one reviewer. The titles were screened for reference to off-label and unlicensed medicine use or adverse drug reactions. Papers relating to specific treatments, conditions or reactions were excluded as well as those relating to prescribing and medication errors. Editorials, notes and letters were also excluded. The remaining abstracts (or papers when no abstract was available) were read and excluded if they made no reference to ADRs in the context of off-label or unlicensed medicine use. The studies identified for inclusion in this review are summarised in Tables 1 and 2.

Description of studies

Authors' definitions

The definitions used by the different authors, together with the setting of the studies varied, and these should be taken into account when interpreting the results of each study.

ADR definition

Only 4 of the 14 studies included gave a definition of an ADR [6–8, 20], each using the WHO definition [9]. Since this definition states that an ADR is "any response to a drug which is noxious and unintended and that occurs *at doses used in man for prophylaxis, diagnosis or therapy*" we can assume that the authors who used it excluded errors and accidental poisonings. The results of studies which did not provide a definition of ADR need to be considered in context: some ADRs may have been excluded resulting in an underestimation of ADR prevalence. On the other hand, the definition may also have been expanded to include reactions resulting from prescription or administration errors or from accidental poisonings, which would have resulted in an overestimation.

Off-label medicine use definition

Only 1 of the 14 studies did not provide a specific definition of off-label use [10]. Turner et al. defined six possible types of off-label medicine use: administered at a greater dose than recommended in the MA, at a greater frequency than recommended, for an indication not described, to a child outside the age range specified, via a route not described and when a contra-indication was described [11, 12]. One other study used these exact definitions [13], while six studies used broadly similar definitions [6–8, 14–16]. Neubert et al. [7] used a retrospective approach to classify medicines as off-label or unlicensed. The information available to them did not include an indication for the use of the medicine and the formulation administered was not always recorded. In the absence of an indication, off-label classification was based

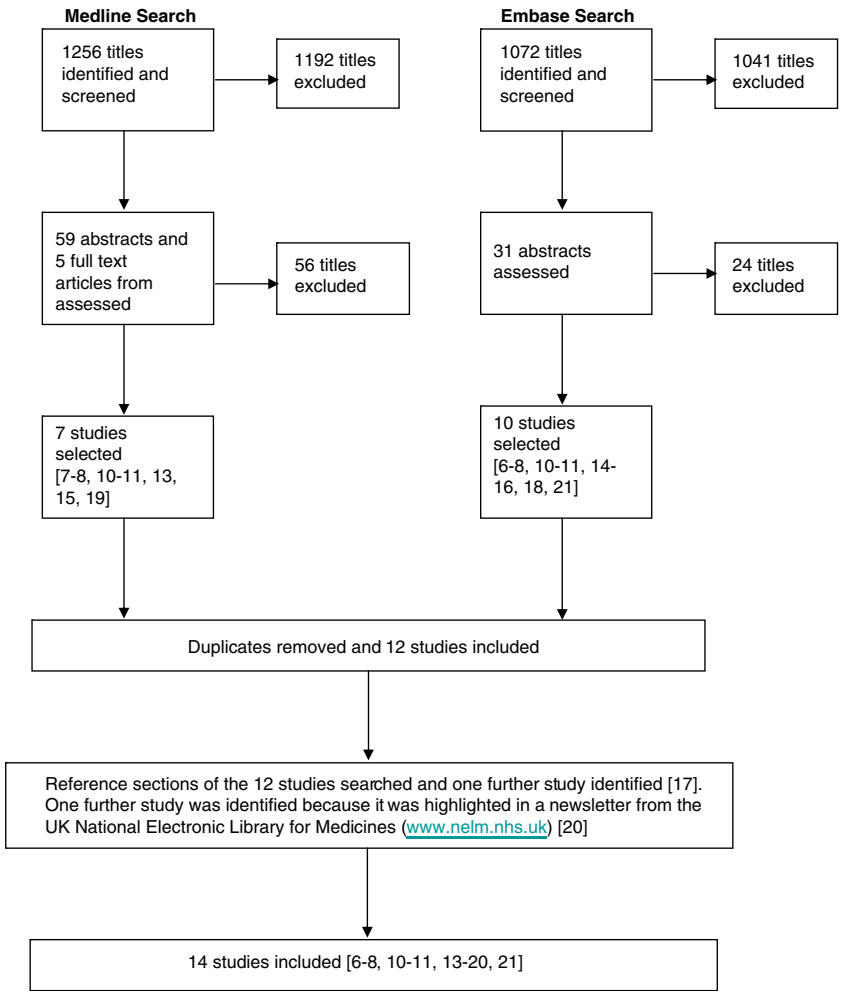

Fig. 1 Method of selection for papers for included in this review

on age, route and maximum dose for any indication. Gill et al. described only three possible types of off-label medicine use: at different dose, for an indication not described, in a child outside the age range specified, but they did not record their reference source [17]. Jonville-Bera et al. described off-label use as use outside at least one of the recommendations in the SPC, specifically: duration of treatment, dose adaptation, precautions for use, monitoring of treatment, absolute contraindication, indication or route [18]. A Swedish study that used data from the medicines information database included the following in their definition of off-label use: not recommended in children, indication not described, outside the age range specified; they used a national prescribing reference [19]. Schirm et al. defined off-label use as the use of medicines not authorised for use in children or in a child under the minimum recommended age; however, they did not consider dose, frequency, route or indication and did not record their reference source [15]. The most recent study defined off-label use as use in children below the recommended age group listed in the SmPC [20].

Unlicensed medicine use definition

Of the 8 studies that considered unlicensed medicine use in addition to off-label use, 4 provided a definition of an unlicensed medicine [11, 13, 16, 19]. Again, Turner et al. and Clarkson et al. used identical definitions as follows: modification to licensed medicines, e.g. extemporaneous preparations, licensed medicines in a modified formulation manufactured under a special manufacturing license, new medicines available under a special manufacturing license, chemicals used as medicines, medicines used before a license had been granted or imported medicines (i.e. licensed in another country) [11–13]. Kimland et al. categorised any medicine not in their national prescribing reference (Swedish catalogue of medical products—FASS) as an unlicensed medicine [19]. A study carried out in Brazil used the following definitions: medicines contra-indicated for use in children, extemporaneous preparations manufactured or modified by a hospital or nurse or medicines for which safety and efficacy in children was not established [16].

Table 1 Summary of prospective adverse drug reaction (ADR) studies

Reference	Year of publication	Duration	Setting	Study design	Primary outcome	Number of patients	Number of ADRs detected	Patients experiencing an ADR	Percentage of prescriptions off-label or unlicensed	Percentage of patients receiving off-label or unlicensed medicines	Observation on association between off-label or unlicensed prescriptions and ADRs
[10]	1985	1 year	A single general paediatric group practice, Canada	Intensive telephone surveillance programme of all patients who received prescriptions	Incidence of ADRs secondary to prescription and non-prescription medicines	3,181 children, 4,244 courses of treatment	Adverse symptoms in 473 courses (11.1%)	–	–	–	Dosage above the total daily dose recommended by the manufacturer was a risk factor for ADR.
[17]	1995	28 months	Paediatric intensive care unit (UK)	Spontaneous ADR reports and chart review	Incidence of ADRs	909	76	7%	–	–	33% of all medicines implicated in an ADR were off-label or unlicensed
[11]	1999	13 weeks	Paediatric hospital including PICU and neonatal surgery (UK)	Spontaneous ADR reports and chart review	Incidence of ADRs to unlicensed and off-label drugs	936 of 1,046 received medicine	–	12.4% of those who received medicine	35% of prescriptions	48% of admissions received at least one	6% of off-label and unlicensed prescriptions were implicated in an ADR (vs 3.9% of licensed prescriptions)
[14]	2002	5 months	Community paediatric practice (France)	Follow-up of randomly selected patients by community paediatricians.	Investigate the potential relationship between off-label drug use and increased ADR risk	1,419	–	1.4%	18.9% of prescriptions off-label	42% of patients received at least one off-label medicine	In the subpopulation of patients who received at least one off-label medicine the ADR incidence was 2%
[6]	2000	9 months	Paediatric ward, included reactions to medicines administered before admission (Italy)	Active monitoring	Identify ADRs related to off-label drug use and evaluate	1,619	41	2.53%	–	–	39% of all ADRs involved an off-label medicine
[7]	2004	8 months	10-bed paediatric ward (Germany)	Weekly review of patient charts	Investigate the extent of unlicensed and off-label drug use and relationship between ADRs and unlicensed and off-label drugs	156 of 178 received medicine		19.9% of those who received medicine	0.4% of prescriptions unlicensed, 26.3% off-label, 3.4% unclassified	51.7% of patients received at least one off-label or unlicensed medicine	6.1% of off-label or unlicensed prescriptions were implicated in an ADR (vs 5.6% of licensed prescriptions)

Table 1 (continued)

Reference	Year of publication	Duration	Setting	Study design	Primary outcome	Number of patients	Number of ADRs detected	Patients experiencing an ADR	Percentage of prescriptions off-label or unlicensed	Percentage of patients receiving off-label or unlicensed medicines	Observation on association between off-label or unlicensed prescriptions and ADRs
[16]	2008	5 months	36-bed paediatric ward (Brazil)	Daily ward visit by clinical pharmacist, review of medical records, attendance on clinical rounds	To obtain information on prescribing patterns, to determine the extent of off-label and unlicensed drug use and to investigate the potential relationship with ADRs	272, 265 of whom received medicine	47	33 children had at least one ADR	5.5% unlicensed, 39.6% off-label	82.6% received unlicensed and/or off-label drugs	ADR incidence was 12.5% in whole study population and 16.3% in patients exposed to at least one off-label drug

Study methods and results

Prospective studies

A summary of the 7 prospective studies published between 1985 and 2008 included in this review is provided in Table 1. Only 2 of these provided a definition of adverse drug reaction [6, 7], both using the World Health Organisation (WHO) definition [9]. Five studies were set in paediatric hospitals and 2 were in community settings, all employed active patient monitoring and the duration of these studies ranged from 13 weeks to 28 months.

Prospective inpatient studies Where it was recorded, the ADR incidence in the prospective inpatient studies ranged from 2.53 to 19.9% [11, 17]. One study found a statistically non-significant increase in ADR risk with off-label and unlicensed medicines (RR 1.74, 95% CI 0.89, 3.41, $p<0.106$) [11]. Another study found that 11 out of 29 inpatients and 5 out of 12 admissions had ADRs attributed to off-label medicines, but the study size was too small to show a significant association. However, in the same study, a significant association was found between off-label medicine use and ADRs requiring pharmacological intervention (RR 7.0, $p<0.04$) [6]. Santos et al. found that off-label medicine use was associated with ADRs (RR 2.44, 95% CI 2.12, 2.89, no p value) [16].

Prospective community-based studies The ADR incidence recorded by Horen et al. was 1.4% of all patients and was 2% in patients receiving at least one off-label medicine [14]. The other community-based prospective study found an ADR incidence of 11.1% in the study population and an increased relative risk of probable or definite ADRs in patients receiving a total daily dose of medicine above that recommended by the manufacturer (7% vs 4.3%; RR 1.63; CI 1.23 to 2.16; $P<0.001$) [10].

Retrospective studies

A summary of the 7 retrospective studies published between 2004 and 2011 and identified for inclusion in this review is provided in Table 2. Two of these studies [8, 20], used the World Health Organisation (WHO) definition of ADRs, while none of the rest of the studies provided a definition. All the studies included ADR reports or queries to either national or regional centres. One study focussed on paediatric reports from hospitals [13]. A limitation that is common to all of these studies is that they are unlikely to provide a representative sample of medicine use and ADR occurrence in a population. The duration of these studies ranged from 5 months to 10 years.

Table 2 Summary of studies that reviewed spontaneous ADR reports/queries

Reference	Year of publication	Duration	Country & source of reports	Study design	Primary outcome	Number of reports / queries	Number of ADRs	Observation on association between off-label or unlicensed prescriptions and ADRs
[8]	2004	1 year	Sweden, national spontaneous report database	Retrospective review of spontaneous reports involving individuals <16 years. Excluding reports of reactions to over the counter medicines, vaccines given at vaccine centres and medicines administered in hospital	Investigate extent and characteristics of off-label prescribing among drugs reported to have caused an ADR	112	158	Off-label use implicated in 42.4% of ADRs
[15]	2004	7 years	Netherlands, national spontaneous report database	Retrospective review of spontaneous reports involving individuals <16 years. Excluding reports of reactions to vaccines. Compared with overall use of off-label and unlicensed medicines from a regional community pharmacy database	Describe ADRs in children outside the hospital	773	–	24% of implicated medicines off-label (vs 23% off-label in the general population), 1.9% of implicated medicines unlicensed (vs 14.6% unlicensed in the general population)
[13]	2004	3 years	UK, regional spontaneous report database containing stimulated reports concerning paediatrics	Retrospective review of spontaneous reports	Raise awareness and stimulate reporting of ADRs in children	456 (242 used for analysis)	–	Off-label or unlicensed use implicated in 27% of ADRs
[21]	2005	5 months	France, regional spontaneous report database	Retrospective review of spontaneous reports	Identify the frequency of "incorrectly used" drugs involved in ADRs and compare with the frequency of "correctly" used drugs involved in ADRs	182	–	75% of all incorrectly used medicines implicated in an ADR (vs 59% of all "correctly used" medicines)
[19]	2007	10 years	Sweden, database of enquiries to a hospital drug information department	Retrospective review of drug information centre queries	Characterise questions and answers regarding drug-related problems and off-label drug treatment	249 queries. 24% about unlicensed use and 31% about off-label use.	91 queries related to ADRs	17% of ADR queries related to unlicensed medicines. 27% of ADR queries related to off-label use
[18]	2009	1 year	France, regional spontaneous report database	Retrospective review of spontaneous reports	Describe the type and frequency of avoidable ADRs following inappropriate prescribing	360 (294 adults and 66 children)	–	32% of ADRs were associated with off-label medicine use
[20]	2011	10 years	Denmark, national spontaneous report database	Retrospective review of spontaneous reports	Identify ADRs associated with off-label prescribing	4,388 reports	–	17% of ADRs were associated with off-label medicine use

Jonville-Bera et al. reported that 75% of off-label prescriptions resulted in an ADR compared with 59% of the approved prescriptions [21]. Schirm et al. were the only authors who attempted to describe the prevalence of off-label and unlicensed medicine use in the general population—they specify that in their study of Dutch community pharmacies, unlicensed medicines would have only included pharmacy preparations. They found that 24% of medicines implicated in spontaneously reported ADRs were off-label and 1.9% were unlicensed [15]. Four studies reported that between 17 and 42.4% of spontaneous ADR reports were associated with off-label medicine use [8, 13, 18, 20]. The study that considered medicine information queries relating to ADRs found that 27% involved off-label medicines and 17% involved unlicensed medicines [19]. A study of spontaneous paediatric reports from hospitals observed that 6 out of 10 medicines implicated in fatalities were off-label or unlicensed [13].

Concluding remarks

Although the results of previous studies have indicated that there may be some association between off-label and unlicensed medicine use and ADR risk [11, 16], there is still a lack of clarity. This stems from the fact that some of these previous studies were small, they employed different methodologies as well as inexact and varying definitions.

There is a need for further research in this area, in particular to ensure that studies are of adequate power to answer some key questions. One of these questions is whether the risk factors for off-label prescribing and those for ADRs converge. The risk factors for ADRs have been discussed above. Off-label and unlicensed medicine use has been found to be more prevalent in certain specialities, e.g. ophthalmology, cardiology and dermatology, in infants, in children who consult their general practitioner more often, receive more prescriptions or have more specialist referrals than other children [22, 23].

Recommendations

Further studies in this area are required and they need to be designed with attention to detail to ensure that the results are reliable, interpretable and useful. Clear definitions of ADR, off-label and unlicensed medicine use should be provided. In our view, the definitions originally provided by Turner et al. [12] are the most comprehensive and unambiguous definitions published. This is borne out by the fact that they have been used by a number of other authors [6–8, 13–16]. That is not to say that these definitions may not need to be modified to suit the study setting; indeed some of the authors who employed them made modifications. If off-label and unlicensed medicine use is categorised using these definitions it should be possible to use the results of future studies to test hypotheses on the reasons why off-label and unlicensed medicine use may be implicated in ADRs, for example: are certain types of off-label or unlicensed medicine use more likely to be implicated in an ADR than others?

Acknowledgments, competing interests, funding This report/article presents independent research commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme (RP-PG-0606-1170).

JM is funded via this programme grant. MP is a NIHR Senior Investigator. MP also wishes to thank the DH (NHS Chair of Pharmacogenetics), MRC, Wellcome Trust and EU-FP7 programme for grant support. MP is a member of the Commission on Human Medicines and Chairs the Pharmacovigilance Expert Advisory Group.

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, NIHR, the Department of Health or any of the other institutions that the authors represent.

References

1. Cuzzolin L, Atzei A, Fanos V (2006) Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Expert Opin Drug Saf 5:703–718
2. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M (2001) Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 52:77–83
3. Clavenna A, Bonati M (2009) Adverse drug reactions in childhood: a review of prospective studies and safety alerts. Arch Dis Child 94:724–728
4. Medicines for Children. In: . http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm#3. Accessed 17 January 2011
5. ADRIC Programme Website. In: . http://www.adric.org.uk. Accessed 06/02 2011
6. Impicciatore P, Mohn A, Chiarelli F, Pandolfini C, Bonati M (2002) Adverse drug reactions to off-label drugs on a paediatric ward: an Italian prospective pilot study. Paediatr Perinat Drug Ther 5:19–24
7. Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, Brune K, Hinz B (2004) The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. Drug Saf 27:1059–1067
8. Ufer M, Kimland E, Bergman U (2004) Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf 13:147–152
9. World Health Organisation (1972) International drug monitoring: the role of national centres. WHO Tech Rep Ser
10. Kramer MS, Hutchinson TA, Flegel KM, Naimark L, Contardi R, Leduc DG (1985) Adverse drug reactions in general pediatric outpatients. J Pediatr 106:305–310
11. Turner S, Nunn AJ, Fielding K, Choonara I (1999) Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 88:965–968

12. Turner S, Choonara I (1997) Unlicensed Drug Use in Children in the UK. Paediatr Perinat Drug Ther 1:52–55
13. Clarkson A, Conroy S, Burroughs K, Choonara I (2004) Surveillance for adverse drug reactions in children: a paediatric regional monitoring centre. Paediatr Perinat Drug Ther 6:20–23
14. Horen B, Montastruc JL, Lapeyre-Mestre M (2002) Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol 54:665–670
15. Schirm E, Tobi H, van Puijenbroek EP, Monster-Simons MH, de Jong-van den Berg LT (2004) Reported adverse drug reactions and their determinants in Dutch children outside the hospital. Pharmacoepidemiol Drug Saf 13:159–165
16. Santos D, Clavenna A, Bonati M, Coelho H (2008) Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. Eur J Clin Pharmacol 64:1111–1118
17. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I (1995) Adverse drug reactions in a paediatric intensive care unit. Acta Paediatr 84:438–441
18. Jonville-Bera AP, Saissi H, Bensouda-Grimaldi L, Beau-Salinas F, Cissoko H, Giraudeau B, Autret-Leca E (2009) Avoidability of adverse drug reactions spontaneously reported to a French regional drug monitoring centre. Drug Saf 32:429–440
19. Kimland E, Bergman U, Lindemalm S, Bottiger Y (2007) Drug related problems and off-label drug treatment in children as seen at a drug information centre. Eur J Pediatr 166:527–532
20. Aagaard L, Hansen EH (2011) Prescribing of medicines in the Danish paediatric population outwith the licensed age group: characteristics of adverse drug reactions. Br J Clin Pharmacol 71:751–757
21. Jonville-Bera AP, Bera F, Autret-Leca E (2005) Are incorrectly used drugs more frequently involved in adverse drug reactions? A prospective study. Eur J Clin Pharmacol 61:231–236
22. Schirm E, Tobi H, de Jong-van den Berg LT (2003) Risk factors for unlicensed and off-label drug use in children outside the hospital. Pediatrics 111:291–295
23. ‘t Jong GW, Eland IA, Sturkenboom MC, van den Anker JN, Stricker BH (2003) Determinants for drug prescribing to children below the minimum licensed age. Eur J Clin Pharmacol 58:701–705