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EAP STATEMENT

Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology

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Abstract

Health-care professionals who prescribe medicines have the professional duty to choose medicines that are in the best interest of their individual patient, irrespective if that patient is an adult or a child. However, the availability of medicines with an appropriate label for pediatric use is lagging behind those for adults, and even available pediatric drugs are sometimes not suitable to administer to children. Consequently, health-care professionals often have no other option than to prescribe off-label medicines to children. An important reason for use of off-label medicines is to improve access to (innovative) treatments or to address medical needs and preferences of patients, especially when no other options are available. However, off-label use of medicines is in general not supported by the same level of evidence as medicines licensed for pediatric use. This may result in increased uncertainty on efficacy as well as the risk for toxicity and other side effects. In addition, liability may also be of concern, counterbalanced by professional guidelines.

Conclusion: The purpose of this joint EAP/ESDPPP policy statement is to offer guidance for HCPs on when and how to prescribe off-label medicines to children and to provide recommendations for future European policy.

Keywords Off-label medicines · European guidance · Rational medicine use · Pediatrics

List of abbreviations

BNF-c	British National Formulary for Children
CJEU	Court of Justice of the European Union
EAP	European Academy of Pediatrics
ESDPPP	European Society for Developmental Perinatal and Pediatric Pharmacology
GP	General practitioner
HCP	Health-care professional

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PICU	Pediatric intensive care unit
PTLD	Post-transplant lymphoproliferative disease
NICU	Neonatal intensive care unit
NKFK	Dutch Expertise Centre for Pharmacotherapy in Children
RTU	Recommendations for use
SmPC	Summary of product characteristics

Introduction

Health-care professionals (HCPs), in close collaboration with pharmacists, who prescribe medicines, have the professional duty to choose medicines that are in the best interest of their individual patient. However, the availability of medicines with an appropriate label for pediatric use is lagging behind those for adults, and available pediatric drugs are often not suitable to administer to children [1]. As a result, HCPs often have no other option than to prescribe medicines to children outside the approved conditions for age, therapeutic indication, dose recommendation, formulation, and/or route of administration (i.e., off-label use [2]) or to prescribe a drug which has not received a license for use in adults or children (i.e., unlicensed medicines use [2]). The practice of off-label prescribing of medicines to children is substantial, both in hospital care and primary health care [3]. A recent report on the setting in the European Union indicates that off-label use of medicines in children is still widespread. Off-label use varies among European countries, with 13–69% of prescriptions being off-label in the hospital setting and 2–100% in primary care [4].

European guidelines on off-label use of medicines in children could greatly benefit children, parents, and their HCPs. Therefore, the purpose of this joint policy statement – endorsed by both councils of the European Academy of Pediatrics and the European Society for Developmental Perinatal and Pediatric Pharmacology – is to offer guidance for these HCPs and to provide recommendations for any future European policy.

European views on off-label use of medicines

According to recent survey findings among European stakeholders, off-label use of medicines is perceived to have both advantages and disadvantages. An important advantage is the accelerated access of patients to (innovative) treatments and the appropriate treatment of medical conditions in patients, when no other options are suitable. On the other hand, the issue of liability in case of negative consequences of off-label use is a widely recognized concern as a formal assessment of safety and efficacy by the relevant authorities has not been performed. Furthermore, friction between national authorities and the pharmaceutical industry may occur if economic reasons are prevailing [4].

The development of medicines for children is complicated by a small and heterogeneous market and methodological and ethical requirements specific for pediatric trials [5]. As a result, many medicines are not labeled for use in children. In order to improve this situation, there have been a number of initiatives, including the European Pediatric Regulation. It has been estimated that more than 50% of medicines used in children have not been tested for the specific age group [6]. In addition, medicines labeled for use in children may underperform with respect to their ability to provide the recommended dose, the suitability of the dosage form, and the presence of potential harmful excipients [7]. For example, the availability of melting or chewable tablets, more likely taken by younger children, appears to be limited [1]. Typical therapeutic areas of off-label use in children include – but are not limited to – infectious diseases, cardiology, dermatology, pain treatment, alimentary tract and metabolism, the respiratory system, and the central nervous system [4]. The highest frequency of off-label use of medicines is seen in patients treated in the NICU, PICU, and children with oncologic diseases.

By using off-label medicines, prescribers, children, and their families have more treatment options to discuss in order to provide a treatment that one finds most appropriate for the needs of the individual patient. In addition, based on the newest available scientific evidence, (innovative) medicines (type of drug, dose, and/or indication) can be prescribed to patients at an earlier stage before the required regulatory approval has been finalized or adopted [4]. However, as off-label use of medicines are in general not supported by the same level of preclinical and clinical evidence as medicines licensed for pediatric use, this may result in increased uncertainty on efficacy as well as the risk for toxicity [7], and prescribers and patients have less information at their disposal to decide to choose (prescriber) or accept (patient) the off-label treatment [4]. Finally, the issue of liability may also be a concern, though often counterbalanced by available professional guidelines [4].

Off-label prescribing is not regulated by European law [9]. European legislation only regulates the marketing of medicines and not the way medicines are ultimately used in clinical practice, which is a national competence or is captured in paralegal statements or guidelines on good practice. Prescribing on-label or off-label medicines is a decision taken within the relationship between a patient and the prescriber. The professional setting (both legal and paralegal) does not limit the right of prescribers to prescribe medicines to "on-label" prescriptions only, as this would in many cases lead to a conflict of professional duties. Therefore, in practice, at the national level, off-label use of medicines is often ethically and legally "accepted" under restrictions.

Several European countries have adopted special statutory regulations for off-label use of medicines and have good practice or professional guidelines for use, including reimbursement decisions (Tables 1, 2, 3). These regulations or policy tools aim for improvement of knowledge regarding efficacy and safety of off-label use. This regulation to encourage pharmaceuticals to file a license extension and/or to create the opportunity to apply research results immediately in a licensed setting is counterbalanced by the uncertainties related to reimbursement practices. In countries where no policy tools are in place, the predominant argument is that off-label use of medicines is an issue that should be dealt with in the context of the relationship between prescriber and patient rather than at level of the regulatory or health-care system [4].

European policy statement on prescribing off-label or unlicensed drugs to children

Off-label use of medicines is subject to several conditions. According to the Court of Justice of the European Union (CJEU), off-label use should remain exceptional in order to preserve the practical effect of the licensing procedure for medicines. Prescribing off-label medicine (1) should be limited to individual situations justified by medical considerations, (2) should be under the responsibility of the prescriber, (3) presupposes that the medicine is necessary to address the needs of the patient, (4) should follow a full assessment and examination of the patient, and (5) should be decided on the basis of purely therapeutic considerations [4].

Table 1 National temporary recommendations for off-label use of medicines[a]

Country	When off-label prescribing?	How?
Belgium	The evaluation of the individual practitioner's choice implies an evaluation of possible alternatives, including alternative treatments, alternative medicinal treatments, and alternatives to a treatment, but in essence, there is "therapeutic freedom"	After informed consent of the parents and patient and after clinical examination
France No. 2011–2012 act (RTU)	If prescriber deems it necessary for patient, given scientific knowledge and absence of available alternative treatment Or If medicine is part of "Recommendations for use (RTU)" scheme. An RTU for off-label use can be issued by the French Agency if certain criteria are met	Prescriber must justify choice Informed consent is required If medication is part of RTU: prescriber should mention this on prescription so that pharmacists can control prescription in this context. The marketing authorization holder should set up patient follow-up RTU medicines are reimbursed by the national health insurance
Italy National Law n. 94/98 (Di Bella Law), 648/96 National Law	If indication relates to therapeutic area with unmet medical need, companies do not want to perform clinical trials for given indication	Off-label use requires support of phase II completed study Informed consent is required; Reimbursed if application of law 648/96
Spain National Royal Decree No. 1015/2009	Off-label use has to be exceptional and only limited to those situations in which no approved alternative exists, with respect to any restriction of the conditions for prescribing and dispensing established in the authorization and the therapeutic protocol of the center	Prescriber has to justify need in the clinical history Informed consent is required Prescriber must notify adverse events Prescriber must comply with established recommendations and therapeutic protocols
Switzerland Federal law on medicinal products and medical devices, Art 9, Art 26	If it is proven that there is no authorized or available alternative medicine that is applicable and equivalent	
Hungary Art 25 of Act XCV (2005), subsection 6	(1) If treatment with licensed medicine is not possible or unsuccessful Or (2) Access to licensed medicine is inhibited to an extent that would likely delay treatment	Prescriber must ensure that: Based on experimental evidence, medicine offers potential of successful treatment or improve/stabilize patient condition; medicine is licensed for distribution in Hungary or another country; prescriber is specialist in specific therapeutic area; prescriber's request for use of this medicine in specific patient has been granted by government body for pharmaceuticals. Risk/benefit balance of off-label medicine is better than that of the licensed medicine; based on experimental evidence, medicine offers potential of successful treatment or improve/stabilize patient condition; the SmPC of licensed medicine does not contain contra-indication regarding requested unlicensed indication

Table 2 National measures to regulate reimbursement of off-label medicines[a]

Country	When off-label prescribing?	How?
Belgium	There is a Special Solidarity Fund for individual patients, but the fund has limited resources. This is because the Belgian reimbursement regulation is based on a positive list of reimbursed products. Consequently, off label can potentially qualify for reimbursement, not necessary linked to an indication or age category. However, the request for addition of a medicinal product to the positive list is the sole responsibility of the marketing authorization holder	
Hungary		Case-by-case evaluation: decision to reimburse is taken based upon circumstances (including existing alternatives and reasons why these are not sufficient) and costs
Germany Section 92 para (1) Nr. 6 SGB V		The German Agency decides if off-label medicines are reimbursed based on a scientific evaluation by its off-label expert commissions. Costs should be refunded also if there are only weak references for efficacy, on condition that the patient suffers from a life-threatening condition and alternatives are missing
Greece Official Gazette 545/B′/01-03-2012 Law 4316/2014		Ministerial decree is required in special cases and according to international bibliographic references Off-label indications could be reimbursed if included in therapeutic protocols approved by the Central Committee of Health Council

HCPs who prescribe off-label medicines to children should comply with ethical and professional standards. Divergence in drug and social laws and institutional and professional rules across Europe may complicate a uniform approach to prescribing off-label medicines in children. Nevertheless, the European Academy of Pediatrics and the European Society for Developmental Perinatal and Pediatric Pharmacology strongly recommend that the following conditions are considered when prescribing off-label medicines to neonates, infants, children, or adolescents. We hereby suggest that this may serve as a checklist for good practice.

Condition #1 All other options, including the use of medicines approved by the regulatory authorities, are unavailable, not tolerated, less optimal, too expensive, not reimbursable by insurance companies, or containing potentially harmful excipients.

Off-label use is not the same as off-knowledge use.

Condition #2 The prescriber is competent to prescribe off-label medicines in children.

An off-label medicine can only be prescribed by someone who has prescribing skills (rational drug therapy) and is knowledgeable about off-label use of medicines in children [10]. As children differ from adults with regard to disease etiology, pharmacokinetic and pharmacodynamic factors, and formulation acceptance, the prescriber should have specific knowledge and experience in the field of pediatrics. Although most HCPs appear to be familiar with the practice of off-label prescribing, most are not aware that the medicines they prescribe are indeed off-label medicines [11]. As this may have consequences for the monitoring of efficacy and adverse events, it is crucial that the prescriber should be aware that he or she is prescribing the medicine in an off-label manner.

Condition #3 Off-label prescription of the medicine is appropriate to meet the needs of the individual patient within the available resources.

There are several situations in which it may be necessary to prescribe a medicine in an off-label manner.

- There may be a medical need where there is no labeled medicine available [4], or the labeled formulation or dosage is not age-appropriate. For example, most medicines used in neonatology have not been tested for the appropriate age and weight group, and most doses have been extrapolated from adult and older children. Moreover, the risk of administration errors can be reduced if age-appropriate off-label drug formulations are prescribed. In addition, off-label use is the rule and not the exception in patients with rare diseases, like clobazam for epilepsy in Dravet syndrome.
- Certain medicines may be licensed, available, and suitable for use in children in one country, but not in another; for example, midazolam oral suspension that is available in Germany but not in Belgium, despite being licensed at the European level.

Table 3 National guidance to professionals on off-label medicine use in children[a]

Country	When off-label prescribing?	How?
Belgium		When a suitable tested and approved alternative is available, prescribing physicians' liability may be at (increased) risk if safety issues arise. If an adverse event arises through the use of that drug, the treating physician would have the burden of proof to demonstrate that its use was performed as standard of care. Key characteristics: usual or common practice, scientific basis, and informed consent
Lithuania Law of Pharmacy No. X-709 (2006) Law of Patients' rights, safety and compensation of harm No. I-1562 (1996)		Off-label use of licensed medicines is possible based on the decision of a council or group of clinical pharmacologists if applicable. In the outpatient setting, it is possible to prescribe off-label and extemporaneous medicines based on experience and personal decision
Sweden SFS 2010:659 and SFS 2014:821		If there is sufficient scientific evidence and clinical experience to prescribe medicine, informed consent is required
UK Good practice in prescribing and managing medicines and devices, 2013		Prescriber must be convinced that there is sufficient evidence or experience of using medicine to demonstrate its safety and efficacy; NICE publishes evidence summaries for off-label and unlicensed medicines Prescriber has responsibility for prescribing the medicine; prescriber is responsible for overseeing patient's care, monitoring, and follow-up (or should ensure this is done by another suitable physician); prescriber must have clear, accurate, and legible record of prescribed medicines and reasons for prescribing medicine off-label; informed consent is required. Pediatric: Royal College of Paediatrics and Child Health (Rev 2, 2013) [24]: Where available, an appropriate licensed preparation should be prescribed and supplied in preference to an unlicensed preparation. In general, it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain consent of parents, caregivers, and child patients to prescribe or administer unlicensed medicines or licensed medicines for unlicensed applications (off-label)[b]
The Netherlands Art 68 of Medicines Act	If relevant professional body has developed protocols or professional standards with regard to the specific off-label use If protocols or standards are under development, prescriber and pharmacist are required to consult each other.	Pediatric: Dutch Pediatric Society (Rev 4, 2018) [26]: The Dutch Pediatric Society has accepted the National Pediatric Formulary as expert guideline Off-label use is considered appropriate if there is a medical need (no registered medicine available or registered medicine is suboptimal for individual patient) There should be a positive balance between expected efficacy and risks based on available literature and assessed within multidisciplinary setting Informed consent is required unless off-label use is documented in National Pediatric Formulary or in professional guideline The prescribing physician should inform parents/caregivers/child about the benefits and risks of off-label or unlicensed use of medicines Off-label treatment with medicines should be regularly and rigorously monitored and adverse events should be reported nationally

Tables 1- 3[a] Based on information provided by EAP members and data included in [4, 27, 30]; [b] used definitions for off-label and unlicensed use may vary across countries and publications[2] . For example, in the UK, off-label use of drugs is referred to as "unlicensed use of licensed drugs". No data: countries not participating in EU study: e.g., Luxemburg, Norway, Switzerland, Iceland, Latvia, Poland, Romania, Croatia, Albania, Macedonia, Serbia, Bosnia, and Herzegovina.

- The licensed medicine may (no longer) be appropriate (has become obsolete), for example, due to the use of harmful excipients (like ethanol or propylene glycol), and an off-label medicine provides an appropriate alternative to use.
- An off-label medicine may address patient's needs better than the licensed medicine in cases when the licensed medicine is minimally effective or ineffective or causes unacceptable side effects, resulting in lower treatment adherence [4].
- Off-label use may be part of the professional treatment guideline [4], for example, in cases where product summaries have not been updated (yet) despite available evidence [12], such as aminoglycoside dosing in neonates and infants. This type of off-label use allows physicians to use existing medicines in an innovative way, when

evidence exists but formal licensing for children has not taken place (yet) [4], as may be the case in pediatric oncology (e.g., rituximab for treatment of post-transplant lymphoproliferative disease (PTLD)).

Condition #4 The off-label prescription should be rational and clinically appropriate.

As with the use of licensed medications, the prescriber must ensure the off-label prescription is appropriate, i.e., the benefit/risk balance should be deemed positive for the individual patient on the basis of the available evidence [4]. All medicines have associated risks of adverse events. In the case of on-label prescribing, the prescriber can rely on the medicine's evaluation by the competent authorities. In the case of off-label prescribing, the prescriber has to weigh the benefit-risk ratio. Off-label prescribing is considered appropriate if (1) it is justified by best available evidence, preferably based on professional guidelines supported by relevant societies (e.g., national pediatric and/or pharmacist societies); (2) it occurs within the context of a formal research protocol; or (3) it pertains to exceptional use, justified by individual clinical circumstances. If none of these justifications is present, its use is generally not recommended (adapted from [13]).

If off-label prescribing is considered appropriate, the prescriber will not automatically be liable for negative impacts on the patient's health, especially if the off-label use is mentioned in a professional guideline or formulary.

Rational pharmacotherapy requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at a reasonable cost to them and their community [14]. Formularies may be effective in improving rational pharmacotherapy in children [15]. In the UK and the Netherlands, HCPs prescribing medicines to children are guided by information in the British National Formulary for Children (BNF-c) and the Dutch National Formulary for Children. In the Netherlands, the development of this open-access formulary has resulted in the revision of many consensus-based dose recommendations and ensured uniformity in prescribing habits in the Netherlands [16]. However, it is important to emphasize that these formularies have still knowledge gaps, like for optimal use of medicines in preterm neonates.

Condition #5 The patient and **parents/caregivers should be informed and involved.**

When considering prescribing an off-label medicine, both children and their parents/caregivers should have all the appropriate information available, if possible, regarding that medicine.

There is limited published literature about the views of patients, parents, and health-care professionals regarding informed consent in off-label or unlicensed use of medicines in children. In general, most children [17], parents [11, 18], and citizens [19] feel that parents should be informed when a medicine is prescribed in an off-label or unlicensed manner, for example, to create alertness to potential side effects [17]. In addition, most older children feel that they also should be informed [17]. The literature from health-care professionals is more mixed: most health-care professionals in Northern Ireland [20] felt that parents should be informed, whereas hospital-based pediatricians in Scotland did not [21]. Knowledge about off-label or unlicensed use of medicines in children is low among the general public [19] and in different studies of parents of healthy and chronically ill children [11, 18]. A minority of hospital-based pediatricians [21] and of general practitioners [22] (GP) in Scotland informed a child's GP [21] or the parents [22]. Once parents knew that their children were prescribed off-label medicines, parents would ask for a licensed medicine [18, 19], or they would use the medicine with more caution [19]. The percentage of refusal of off-label use was higher among parents of otherwise healthy children compared with parents of chronically ill children [23].

As summarized in Tables 1 and 3, several national policy tools indicate that patients should be informed and provide consent when off-label or unlicensed medicines are prescribed, although it is not always clear to what extent this consent differs from the regular consent procedure**.** The Royal College of Paediatrics and Child Health stated that – when prescribing off-label medicines to children – it is not necessary to take additional steps to obtain consent of parents, caregivers, and children beyond those taken when prescribing licensed medicines [24]. This is in line with the policy statement issued by the American Academy of Pediatrics in 2014, which states that administration of off-label medicines in children does not warrant special consent if it is based on sound medical evidence. Obviously, if the off-label use is experimental as part of a study, then the patient (and/or parent) should be informed of its experimental status and has to provide the study related assent and/or consent [25]. European HCPs should know and abide by the appropriate informed consent laws in their respective countries.

Condition #6 The patient should be monitored for efficacy and adverse events.

Similar to licensed medications but possibly with a heightened vigilance [8], the prescriber and pharmacist should ensure appropriate monitoring. Adverse events should be reported to the national pharmacovigilance system by HCPs but also by the families (parents and or children). In case where medicines are prescribed that have reasonable rationale for use but insufficient evidence to mitigate safety, efficacy, and cost-effectiveness concerns, yet they are not part of clinical research ("innovate off-label use"), then outcomes should be evaluated prospectively, documented appropriately, and reported to all stakeholders (HCPs and patients) in a timely fashion. Regular review should occur to reduce the risk of

continued use that is not efficacious or is unsafe [28]. In this way, this condition is true for any prescription, including off-label or unlicensed use.

Condition #7 The prescriber should consider if off-label prescribing should be part of a clinical trial.

Finally, in order to increase our knowledge about the efficacy and safety of all medicines used in children, prescribers should be informed about clinical trials involving off-label medication in which the patient could participate and inform the parents and – when applicable – also the children.

Policy statement: recommendations

Off-label and unlicensed prescription practices occur. In order to facilitate the clinical practice of appropriate, rational and safe prescribing of off-label medicines to individual children, the EAP and ESDPPP strongly recommend that:

- All HCPs prescribing medicines to neonates, children, or adolescents have access to reliable and up-to-date information (where possible) on the medicine they prescribe. A European pediatric formulary with the best evidence on dosing and safety information could be a useful tool for improving the rational use of medicines in children and adolescents [15]. The BNF-c and the Dutch formulary could serve as templates [16].
- Pediatric clinical pharmacologists/pediatricians/pediatric pharmacists should be actively involved/consulted in decision-making processes by hospital, pharmacotherapeutics committees, and national health-care authorities.
- Enhanced safety monitoring and reporting by parents and caregivers should be promoted when off-label medicines are prescribed.
- Parents and patients but also the public should be educated about off-label and unlicensed use of medicines.
- Where off-label use of a medicine is common and evidence-based, it should be the shared responsibility of marketing authorization holder and the relevant regulatory authorities to take appropriate measures to address legal uncertainty and safety concerns, including updating of the SmPC.
- Health authorities and health insurances should support and thus reimburse therapeutic practices that are evidence-based or advocated by a respectable and responsible body of professional opinion, regardless of labelling status.
- Legislation should be adopted that aims to effectively stimulate research into off-label medicines, including publication of clinical trial data [29]), and facilitate the registration of off-label uses with a positive benefit-harm balance.

Conclusion

HCPs often have no other option than to prescribe medicines to children outside the approved conditions for age, therapeutic indication, dose recommendation, formulation, and/or route of administration. This EAP/ESDPPP policy statement is intended to offer practical guidance to these HCPs on when and how to prescribe off-label medicines to children. Several recommendations should be considered when prescribing off-label medicines. This list of recommendations may serve as a checklist for good practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, ethical approval or informed consent does not apply.

References

1. van Riet-Nales DA, de Jager KE, Schobben AF, Egberts TC, Rademaker CM (2011) The availability and age-appropriateness of medicines authorized for children in the Netherlands. Br J Clin Pharmacol 72:465–473
2. Neubert A, Wong IC, Bonifazi A et al (2008) Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res 58:316–322
3. Kimland E, Odlind V (2012) Off-label drug use in pediatric patients. Clin Pharmacol Ther 91:796–801
4. Weda M, Hoebert J, Vervloet M, et al (2017) Study on off-label use of medicinal products in the European Union. https://nivel.nl/sites/default/files/bestanden/Report_OFF_LABEL_Nivel-RIVM-EPHA.pdf
5. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK (2014) Pediatric drug formulations: a review of challenges and progress. Pediatrics 134:361–372
6. European Medicines Agency (2016). 10-year report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation EMA/231225/2015

7. Tuleu C, Breitzkreutz J (2013) Educational paper: formulation-related issues in pediatric clinical pharmacology. Eur J Pediatr 172:717–720
8. Bellis JR, Kirkham JJ, Thiesen S et al (2013) Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. BMC Med 11:238
9. European Court of Justice, T-452/14 Laboratoires CTRS v Commission, paragraph 76. http://curia.europa.eu/juris/liste.jsf?num=T-452/14&language=EN
10. Curriculum for common trunk training in paediatrics. Agreed by the general assembly of EAP in Brussels, 6 December 2014. http://eapaediatrics.eu/wp-content/uploads/2015/12/Agreed-Common-trunk-curriculum-training-LAST1.pdf
11. Balan S, Hassali MA, Mak VS (2015) Awareness, knowledge and views of off-label prescribing in children: a systematic review. Br J Clin Pharmacol 80:1269–1280
12. Pandolfini C, Campi R, Clavenna A, Cazzato T, Bonati M (2005) Italian paediatricians and off-label prescriptions: loyal to regulatory or guideline standards? Acta Paediatr (Oslo, Norway : 1992 94: 753–757
13. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ (2006) Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust 185:544–548
14. World Health Organization (1985). The rational use of drugs. Report of the Conference of Experts Geneva
15. Bonati M, Pandolfini C (2004) Is it time for a European formulary of paediatric medicines? Arch Dis Child 89:890–891
16. van der Zanden TM, de Wildt SN, Liem Y, Offringa M, de Hoog M (2017) Developing a paediatric drug formulary for the Netherlands. Arch Dis Child 102:357–361
17. Mukattash T, Trew K, Hawwa AF, McElnay JC (2012) Children's views on unlicensed/off-label paediatric prescribing and paediatric clinical trials. Eur J Clin Pharmacol 68:141–148
18. Bang V, Mallad A, Kannan S, Bavdekar SB, Gogtay NJ, Thatte UM (2014) Awareness about and views of parents on the off-label drug use in children. Int J Risk Saf Med 26:61–70
19. Mukattash TL, Millership JS, Collier PS, McElnay JC (2008) Public awareness and views on unlicensed use of medicines in children. Br J Clin Pharmacol 66:838–845
20. Mukattash T, Hawwa AF, Trew K, McElnay JC (2011) Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. Eur J Clin Pharmacol 67:449–461
21. McLay JS, Tanaka M, Ekins-Daukes S, Helms PJ (2006) A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians. Arch Dis Child 91:584–587
22. Ekins-Daukes S, Helms PJ, Taylor MW, McLay JS (2005) Off-label prescribing to children: attitudes and experience of general practitioners. Br J Clin Pharmacol 60:145–149
23. Lenk C, Koch P, Zappel H, Wiesemann C (2009) Off-label, off-limits? Parental awareness and attitudes towards off-label use in paediatrics. Eur J Pediatr 168:1473–1478
24. The use of unlicensed medicines or licensed medicines for unlicensed applications in paediatric practice (2013). Policy statement produced by the joint RCPCH/NPPG Standing Committee on Medicines
25. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, van den Anker J, American Academy of Pediatrics Committee on Drugs (2014) Off-label use of drugs in children. Pediatrics 133:563–567
26. Nederlandse Vereniging voor Kindergeneeskunde (2018). Policy statement of the Dutch expertise Centre for Pharmacotherapy in Children and the Dutch Paediatric Society on the prescription of off-label medicines to children
27. Lenk C, Duttge G (2014) Ethical and legal framework and regulation for off-label use: European perspective. Ther Clin Risk Manag 10:537–546
28. Ansani N, Sirio C, Smitherman T, Fedutes-Henderson B, Skledar S, Weber RJ, Zgheib N, Branch R (2006) Designing a strategy to promote safe, innovative off-label use of medications. Am J Med Qual 21:255–261
29. Schrier L, Illy K, Valiulis A, Wyder C, Stiris T (2018) EAP viewpoint on unpublished data from paediatric clinical trials. Eur J Pediatr 177:275–277
30. Vannieuwenhuysen C, Slegers P, Neyt M, Hulstaert F, Stordeur S, Cleemput I, Vinck I (2015) Towards a better managed off-label use of drugs. Health services research (HSR) Brussels: Belgian health care knowledge Centre (KCE). KCE reports 252. D/2015/10.273/82

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