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EVALUATION OF CASES WITH THE USAGE OF COMMERCIALLY AVAILABLE TABLETS IN THE PEDIATRIC FORMULA

ELŻBIETA KURIATA[1]* and WIESŁAW SAWICKI[2]

[1] Voivodeship Farmaceutical Inspectorate in Olsztyn, Poland
[2] Chair and Department of Physical Chemistry, Faculty of Pharmacy with Subfaculty of Laboratory Medicine, Medical University of Gdańsk

Abstract: Lack of availability, of either the medicinal product intended to be used for children, or such in a dose which is fitting for the individual child's needs, results in physicians administering medicines meant for the adult. The target of the thesis was to evaluate the cases with the usage of commercially avaible conventional tablet-formulated medicinal products intended for the adult in the pediatric formula. The subjects of the evaluation were the form of the pediatric drug, prepared from commercially available tablets and capsules, as well as the legitimacy of their usage in the treatment of the pediatric population. One hundred and fifty-four prescriptions filled in community pharmacies of Warminsko-Mazurskie Voivodeship in 2011 were chosen. A total of 5805 divided powders in starch capsules were prepared. The prescribing practice included 6 groups of manufactured medicinal products in the form of conventional tablets, containing as follows: anti-hypertensive medicines (ACE inhibitors – enalapril, captopril, ramipril, loop diuretics – furosemide, potassium sparing diuretics – spironolactone, ß-adrenolytics – propranolol, α- and β-adrenolytics – carvedilol), medicines for heart failure (foxglove glycosides – digoxin, methyldigoxin), anti-clotting medicines (acetylsalicylic acid), peristalsis stimulating agents (metoclopramide), antibacterial medicines (furagin), and dopaminergic (carbidopa-levodopa). The only compounded forms ordered by the physicians were divided powders for an internal use. Starch capsules for powder preparation provided the only 'package' for the dose of the compounded powder, which after pouring, solving or suspending in water was administered to children. Such a shift of the form, between an oral tablet and divided powder for an internal use, did not cause a change in the method of administration. The information on indications and the way of dosage for children, inserted in the Summary of Product Characteristics, enables the administration which follows the registered indications, despite the shortage of an appropriate dose in the pharmaceutical market. In contrast, an absence of the information regarding the indications and a dosage for children in the Summary of Product Characteristic, results in an off-label administration, in case of a child.

The pharmacotherapy of the child population, which is non-homogenous, occasionally requires the usage of medicinal products initially registered for adults. Enabling the dosage of a manufactured pediatric medicinal product, meant for various body weights, would result in producing many different doses of the medicine formulation. As following, the technological development, the registration process and the multi-dose manufacturing, appear as non-profitable for the manufacturer (1). This is a reason for many medicines, efficient in child treatment, remaining unavailable in an appropriate dose and formulation. Lack of availability, of either the medicinal product intended to be used for children, or such in a dose which is fitting for the individual child's needs, results in physicians administering medicines meant for the adult.

As an example of such practice, the administration of a manufactured tablet in a dose for adults, requires its adjustment to the child's needs, and the splitting of it into smaller portions. Commonly practised is splitting a tablet into two or four parts by the patient or their carer.

Tablets containing perforations are especially meant for such a case. The method, however, is not wholly precise and should be practised neither with strong agents and a narrow therapeutic index, nor with tablets possessing a notably small diameter. Each part of the split tablet may have a different mass, which is in turn connected to specific, albeit varying, contents of the agent.

Another method aimed at adjusting the dose to the child's needs is that of preparing divided powders for an internal use, compounded from conventional tablets. The aforementioned are prepared based on the doctor's prescription, by authorized individuals, in the pharmaceutical conditions such as the formula room, employing usage of the appro-

* Corresponding author: e-mail: e.kuriata@wif-olsztyn.pl

priate scales and utensils. A correct calculation of the amount of tablets to be used for the powder is a vital question. Such a calculation is achieved in relation to a declared amount of the agent in a single tablet. Medicinal substances can be blended with neutral excipients, equipped with filling properties. An increase in the powder mass results, as the used medicinal substance is applied in very small doses. The ready powders are then placed in starch or hard gelatin capsules, as well as in paper sachets. Such a method, however, cannot be used to split modified release tablets. The situation in question could lead to the change of the absorption site and the bioavailability of the medicinal substance.

The following way of the dose adjustment to pediatric needs is solving or suspending the substance (powdered tablet or the content of a capsule) in either a solvent or a dispersing solution.

This is how we achieve liquid forms of drugs which seem to be the most appropriate oral formula addressed to the new-born, infants and younger children. The pharmaceutical market currently offers ready liquid bases, featured with various flavors acceptable to the child's palate.

The disadvantage of this form is a low physicochemical stability of the medicinal substance; a higher, compared with powders, probability of formula incompatibility occurrence; and the growth of microbes in the aqueous surrounding.

Each medicinal product to be marketed in the EU should have complete and up-to-date information before obtaining marketing authorization. This includes the information for patients (Patient's Leaflet) as well as the information for healthcare providers (Summary of Product Characteristics) and labeling (2). Such are the registration documents of the medicinal product manufacturer, necessary to its marketing.

The Summary of the Product Characteristics contains i.a. the following information: the name of the medicinal product; its qualitative and quantitative composition, pharmaceutical form, and therapeutic indications; its posology, and the method of administration for adults and, where necessary, for children (3). The dosage is specified for each method of administration. The European Comission recommends that if the product is indicated in the pediatric population, posology recommendations should be given for each of the relevant subsets. The age limits should reflect the benefit-risk assessment of the available documentation for each subset. If the product is indicated in children and no adequate pediatric formulation can be developed, detailed instructions on how to obtain an extemporaneous preparation should be included in the section dedicated to special precautions for the disposal of a used medicinal product, with a cross-reference in the section for posology and method of administration (4).

The target of the thesis was to evaluate the cases with the usage of commercially available conventional tablet-formulated medicinal products intended for the adult in the pediatric formula.

The subjects of the evaluation were the form of the pediatric drug, prepared from commercially available tablets and capsules, as well as the legitimacy of their usage in the treatment of the pediatric population.

EXPERIMENTAL

The study consisted of the analysis and the evaluation of the compounded drug prescriptions, filled in community pharmacies of Warminsko-Mazurskie Voivodeship in 2011.

The preliminary study embraced 1699 pediatric prescriptions, filled in sixteen community pharmacies. For a further evaluation, the prescriptions with the usage of manufactured tablets meant for adults were chosen. One hundred and fifty-four prescriptions met the above criteria, which constituted 9% of all pediatric prescriptions. One hundred and fifty-four compounded drugs in the form of divided powders for an internal use, in the number placed between 20 and 40 per script, were a result of the aforementioned prescriptions. A total of 5805 divided powders in starch capsules were prepared. The prescriptions for children, containing manufactured tablets, were filled in six pharmacies. This constituted 37.5% of all pharmacies embraced within the study.

RESULTS

Based upon the body of the actual prescription, the authorized personnel, masters of pharmacy or pharmaceutical technicians, prepared divided powders for an internal use.

The preparation of the powders utilized technological processes such as crushing the tablet or pouring the content of a hard capsule and powdering in a mortar; thorough blending with an excipient; proper weighing; and finally, placing into starch capsules with the diameter of 14 mm (No. 2) or of 16 mm (No. 3).

The amount of the excipient used as filler was estimated depending upon the preference of the actual person compounding the medicine. Most

commonly it occurred to hesitate between 0.1 and 0.2 g of dextrose or lactose per unit of powder. The next step took place already in the household conditions, and consisted of emptying the starch capsules from the mixture powder by the children's carers, and stirring or solving it in a small amount of water or milk, and then administering it orally to a child.

The prescribing practice included 6 groups of manufactured medicinal products in the form of conventional tablets, containing as follows: antihypertensive medicines (ACE inhibitors – enalapril, captopril, ramipril, loop diuretics – furosemide, potassium sparing diuretics – spironolactone, β-adrenolytics – propranolol, α- and β-adrenolytics – carvedilol), medicines for heart failure (foxglove glycosides – digoxin, methyldigoxin), anti-clotting medicines (acetylsalicylic acid), peristalsis stimulating agents (metoclopramide), antibacterial medicines (furagin), and dopaminergic (carbidopa-levodopa). Additionally, according to the doctor's order, one of the two excipients were subsequently added to each powder: lactose or dextrose.

The thesis gives both, the analysis and estimate of the following data: the place of the prescribing practice, the doctor's speciality, the patient's age, the content of the compounded drug, its amount and its form. Table 1 shows which of the substances the evaluated amount of pediatric powders contained.

In some patients a few substances were applied at the same time. Each of them was prescribed separately and placed in separate starch capsules. The following combinations of the medicinal substances were reported:

- captopril, carvedilol, spironolactone, β-methyldigoxin
- enalapril, propranolol
- digoxin, captopril, spironolactone
- captopril, spironolactone

The children's ages varied from 2 weeks up to 4 years. The prescribing practice were applied by physicians of the specialities as given: pediatrician, cardiologist, neo-natologist, family doctor, pulmonologist, general practitioner and the non-speciality physician delivering their service within the hospital ward, the outpatient clinic and the hospice home care.

In all studied cases, the same formula of the compounded drug was prepared – divided powders for an internal use in starch capsules, in the number between 20 and 40. For preparation of the compounded drugs were used manufactured medicinal products - ordinary, non-modified release tablets. Moreover, there were used hard capsules filled with a medicinal substance and excipients, as well as hydrophilic membrane tablets – helpful with swallowing and covering up an unpleasant flavor, in case of the latter.

The recommended dosages of active medicines were contained in the Summary of Product Characteristics for each of the following: Captopril Jelfa (2008), Captopril Polfarmex (2008), Enarenal (2007), Axtil (2009), Spironol (2010), Verospiron

Table 1. The occurrence of the medicinal substance in the evaluated amount of compounded pediatric powders.

Medicinal substance	Amounts of powders	% powders (n = 5.805)
Captopril	1870	32.21%
Carbidopa-levodopa	700	12.06%
Spironolactone	660	11.37%
Carvedilol	520	8.96%
β-Methyldigoxin	440	7.58%
Acetylsalicylic acid	365	6.29%
Propranolol	360	6.20%
Enalapril	300	5.17%
Metoclopramide	200	3.45%
Ramipril	160	2.76%
Digoxin	120	2.07%
Furosemide	80	1.38%
Furagin	30	0.52%

(2009), Furosemidum (2008), Propranolol (2008), Carvedilol (2011), Digoxin Teva (2008), Bemecor (2008), Acesan (2010), Metoclopramid (2008), Furaginum (2008), Nacom mitte (2008).

The outcomes of the prescription analysis referred to the ordered medicinal substance; the child's age, the way of dosage of the compounded drugs and the medicinal products used for their preparation, are shown in Table 2.

Hypotensive medicines

Amongst ACE inhibitors only captopril is recommended by the manufacturer to be used with infants and children. Admittedly, there is no manufactured medicinal product in an appropriate dose; the producer, however, gives a thorough description of the pediatric dosage in the registration documents. Captopril is recommended for children with an initial dose of 0.3 mg/kg b.w. and in case of children with kidney dysfunction, preterm infants, newly born and infants with an initial dose of 0.15 mg/kg b.w..

The recommended dosage of enalapril is 2.5 mg for children with body weight between 20 and 50 kg. The medicine is not recommended for the new-born, children and young people with

Table 2. The most frequently prescribed active substances including pharmacological groups, child's age, dosage and commercial medicinal products used to prepare analyzed powders.

Active substance	Child's age	Dosage	Medicinal product used
Hypotensive drugs			
Enalapril	1 - 28 months	0.1-0.65 mg 2 times daily 1 or 2 powders 3 times daily	Enarenal 5 mg × 30 tab.
Captopril	2 – 48 months	1, 2, 3 mg 1, 2 or 3 times daily	Captopril 12.5 mg × 30 tab.
Ramipril	5.5 – 8 months	0.3 mg 1 or 2 times daily	Axtil 2.5 mg × 30 tab.
Furosemide	18 months	2.5 mg 2 times daily	Furosemid 40 mg × 30 tab.
Spironolactone	2 – 12 months	2.0-3.0 mg 1 or 2 times daily	Spironol 25 mg × 20 tab., Verospiron 50 mg × 30 cap.
Propranolol	6 – 12 months	3.0 mg 3 times daily	Propranolol 40 mg × 50 tab.
Carvedilol	2 - 7 months	0.1 or 0.2 mg 2 or 3 times daily	Carvedilol 6.25 mg × 30 tab.
Cardiac drugs			
Digoxin	2 – 3 months	0.015 mg 2 times daily	Digoxin 0.1 mg × 30 tab.
β-Methyldigoxin	2 – 7 months	0.01 mg 2 times daily	Bemecor 0.1 mg × 30 tab.
Anti-clotting drugs			
Acetylsalicylic acid	6 – 17 months	15 mg once daily	Acesan 30 mg × 60 tab.
Peristalsis stimulating drugs			
Metoclopramide hydrochloride	3 years 6 months	2.5 mg 2 times daily	Metoclopramid 10 mg × 50 tab.
Antibacterial drugs			
Furagin	10 months	10 mg once daily	Furaginum 50 mg × 30 tab.
Antiparkinsonism drugs			
Carbidopa-levodopa	4 years	10 mg 2.3 times daily	Nacom mitte

glomerular filtration rate (GFR) < 30 mL/1.73 m^2. In the studied cases the medicine was given to children of the age from 2 weeks up to 28 months. The dosage was determined by the manufacturer based upon the body weight of the child. In contrast, the information about the child's weight was not given in the prescription which is the basis for preparation of a compounded drug. The manufacturer of ramipril does not recommend the usage in cases of children and young people below the age of 18 in relation to the lack of enough safety and efficacy data.

In the evaluated prescriptions for preparation of a compounded drug, one used spironolactone of two manufacturers. The descriptions from the registration documents of both vary subtly as for the usage in children. One of the producers recommends the usage for children and young people below 18 with a saturating dose of 2–3 mg/kg b.w. in 1-4 divided doses and one maintaining dose of 1-1.5 mg/kg b.w. The medicine is possible to crush and then administer with fluid. While the other manufacturer restricts only to a short description: 3.0 mg/kg b.w. once or in two divided doses.

According to the registration documents, furosemide cannot be applied in children who are not capable of swallowing a tablet. In this case, the dosage places between 1 mg and 3 mg/kg b.w. once every 24 h. One must not apply the doses larger than 40 mg per 24 h independently from the child's body mass.

α-Adrenolytics as well as α- and β-adrenolytics were represented by propranolol and carvedilol. The former is recommended for children above 6 at the dose of 20 mg 2-3 times daily. The manufacturer of the latter shows the lack of experience in usage of the drug in case of children and young people.

Cardiac drugs

Digoxin is recommended to be used with infants and children. The manufacturer did not market the pediatric dose, however, they nevertheless described thoroughly the way of dosage in the registration documents - for infants and children up to 2 years old a saturating dose 20-35 μg/kg b.w., with a maintaining dose 5-9 μg/kg b.w., for children 2-12 years old a saturating dose of 10–15 μg/kg b.w., with a maintaining one 3-5 μg/kg b.w..

It was observed that in the case of the other child the doctor ordered β-methyldigoxin. The producer of this medicine in the registration documents does not give any information referring to the safety or unsafeness of the usage with children. The dosage of this drug is related to the adult group only.

Anti-clotting drugs

Acetylsalicylic acid should not be used for children up to 12 years in case of viral infections because of the possibility of Reye's syndrome occurrence.

Peristalsis stimulating drugs

Metoclopramide hydrochloride should not be applied for children below 15 years of age.

Antibacterial drugs

The indications for the application of furagin refer to children over 2 up to 14 in a dose of 5 mg to 7 mg/b.w. 24 h in 2-3 divided doses. A tablet can be crushed and stirred with milk. In case of children below 2 the dose has to be estimated directly by the physician.

Antiparkinsonism drugs

Complex medicines consisting of carbidopa and levodopa are not recommended for patients below 18 years since there is not sufficient data regarding either the safety or the efficacy in infants and children.

DISCUSSION

One of the vital issues of the thesis was verifying and evaluating the way the pharmaceutical market responds to the needs of pediatric pharmacotherapy when faced with the shortage of appropriate forms and doses of a medicinal product. Deduced from the literature the usage of such drug forms as suppositories and per rectum fluids is recommended for the new-born and infants. Starting from the one-month-old liquid forms are preferable, along with those of tablets, granulates or powders which can be administered with drinks or food (1). The researches conducted in 16 European countries in 2003 showed that the methods of preparing a pediatric form and dose varied depending upon the country where the compounded drug was prepared. In Denmark, England, Ireland, Norway and Sweden, liquid forms seem to be preferable. The majority of such are drops, solutions, suspensions, emulsions and sirups (5, 6).

There are still many countries in Europe where pharmacists prepare their own sirups and suspending vehicles due to low cost, local availability, and the policy. Contamination is more likely to occur in a poorly-preserved preparation when a single storage container is placed in and out of refrigeration for multiple sampling during the intended in-use shelf life of an extemporaneous preparation. The use of

commercially available vehicles is recommended (7). For oral liquids in European formulary practice, the universal, commercial suspending vehicles are used (for example: Ora®-products). Such consist of suitable preservatives (methylparaben, potassium sorbate) and flavors, and allow to spare time for preparing formulation, to mask an unpleasant taste and to provide the conditions which make the preparation more stable (8).

There are several studies concerning the stability of medicinal substance in a liquid vehicle which were conducted in the USA and in Europe. Oral pediatric liquids with propranolol, prepared from tablets in a simple sirup with sorbitol and glycerol with no preservative remained stable for at least 35 days, stored either at 25°C or 4°C. Oral pediatric liquids with enalapril maleate, prepared from tablets in a raspberry sirup or 85% orthophosphoric acid solution, remained stable for at least 30 days, stored at 25°C or 4°C. All suspensions contained methyl hydroxybenzoate 0.2% as a preservative (8, 9).

Even if no microbial or fungal growth was observed in the non-preserved medium, there is a lack of any reliable evidence regarding its microbiological stability. Therefore, a storage time exceeding 14 days should be avoided (8, 9).

In Belgium, Croatia, France, Sweden and Switzerland, hard gelatine capsules are a preferred form, whose structure consists of two cylindrical parts, both with rounded ends (5, 6). A powdered substance is placed in one and closed with the fitting other. These capsules are usually intended to be swallowed as a whole; however, in case of infants and young children, one should open a capsule and having its content mixed with a small amount of liquid, administer as a drink (6). In Italy, Finland, Scotland and Portugal, the most commonplace are divided powders (5, 10). Such are packed in paper sachets. All substances, after being powdered and weighed, are put into small, folded paper bags, every single one of which is treated as a unit dose of the drug. The medicine is administered after solving the content in water, milk or other fluid.

In the group of prescriptions, reviewed in the thesis, the only form of a compounded drug prescribed by physicians were divided powders for an internal use. Such powders were prepared with the usage of starch capsules. This form is intended to be swallowed as a whole, which makes it inappropriate for infants and young children. In the referred cases, the aforementioned had to be taken as a specific unit dose 'package' in order to be administered to children, after mixing with drink as a liquid suspension or a solution.

In the actual pharmaceutical formula, the used medicinal products were only non-modified release tablets and plain capsules. After micronization of a tablet, or the content of a hard gelatine capsule, the powders were stirred with an excipient, lactose or dextrose.

The size of the crushed grains of the powder plays a crucial role in the stability of the medicinal substance, among others upon its photochemical stability. The smaller the size of the grains, the more rapidly the photo-degradation rate constant grows. Facing that fact, the usage of lactose was desirable. Lactose is easily prone to a free radicals attack. Most likely, it acts as a free radicals transmitter in order to inhibit the medicinal substance degradation (11).

It should be noted that pharmacy-compounded, divided powders, enabled the application of the pediatric doses which are not manufactured by the pharmaceutical industry. The shift of the form of medication did not change the method of administration, as in all the cases the drug was to be taken orally.

The other analyzed issue was the legitimacy of the usage of the medicinal products being a subject of the study in the treatment of the child population. The manufacturers of medicinal products are obliged in the registration process to prepare the Summary of the Product Characteristics intended for medical personnel, as well as the patient's leaflet, both containing i.a. indications, precautions and the way of dosage of the product. In case of those medicinal products which are in the registration documents intended and precisely described as for the dosage for children, there is no doubt pertaining to their usage. This refers to medicinal products containing captopril, spironolactone, digoxin and furagin. Such group may also include furosemide. The manufacturer does not, however, recommend the drug in case of children who have problems with swallowing a tablet. Although it does appear more profitable for the patients to administer the medicine, in the form of divided powders that are processed into a liquid form in the household conditions by the child's carer. In such a situation, there is no barrier with swallowing the tablet. The appropriate dosage for children was determined by the manufacturer as ranging from 1 to 3 mg/kg b.w.

The problem occurs in case of the pediatric usage of those medicinal products which are not indicated for children, or do not have an appropriate dose. The treatment beyond the indications given in the Summary of the Product Characteristics is named as 'off-label'. Prescribing an 'off-label' medicine results in accepting responsibility for the effect

of its action. A physician can prescribe an 'off-label' drug beyond the medical experiment and clinical trials procedures only if the aforementioned physician does not expect the possibility of such constituting an illegal act, or does not intend the extension of the medical knowledge (to discover or to prove the effect of the drug), and the efficacy of the hitherto applied methods appears to be insufficient (12).

The usage of off-label drugs in the pediatric population is known worldwide. The off-label medicines are applied first and foremost during hospital treatment. For instance, based upon the studies carried out in France among 989 hospitalised patients, it was revealed that 56% of children had one or more off-label status medicines prescribed (13).

Whereas, the Brazilian research conducted upon 61 patients had demonstrated that 27.7% of the prescribed drugs for infants were off-label medication (14). Parallel with these was the Palestinian study, where 35.3% of 387 hospitalized children had the drugs of the same as the aforementioned status prescribed (15).

The preparation of off-label drugs in community pharmacies is most commonly connected with post-hospital treatment and a necessity for continuing hospital-ordained pharmacotherapy.

In the literature, there are four cases of drug usage beyond the strictly registration-adhered indications (16):

1. The usage of a medicinal product in a way which is not mentioned in the registration documents.
2. The usage of a drug following the registered indications in patients for whom there is no dosage determined.
3. The usage of a drug in an indication that is not mentioned in the registration documents, but of which there is reliable data warranting its safety and efficacy.
4. The usage of a drug in a new indication which is not mentioned in the registration document, but of which there is scientific-based evidence warranting its efficacy and safety.

Enalapril (3 cases), propranolol, metoclopramide and acetylsalicylic acid were applied in the patients for whom there is no dosage determined. The registration-related indications of enalapril dosage refer to the child's body weight and recommend the dose of 2.5 mg for a child of 20–50 kg b.w. The data in the prescription give only the child's age, and they should not be compared with the child's body weight; however, the assumption of a two-week- or one-month -old child whose body weight is at least 20 kg does not seem to be acceptable. In the registration documents the manufacturer did not take into consideration children with the body weight below 20 kg. Propranolol is recommended for children above the age of 6. The drug, however, has been administered to a patient between 6 and 12 months old. Metoclopramide should not be used with children below the age of 15. The medicine, though, was administered to a 4-year-old child. The registration documents of acetylsalicylic acid do not contain the dosage for children. The other remaining substances i.e., ramipril, carvedilol, methyldigoxin and carbidopa-levodopa do not have registration indications applying to the treatment of children.

In the aforementioned situations, the medicines which were administered to children had an 'off-label' status. In cases of some indications, the Polish Ministry of Health accepts the usage of 'off-label' drugs and refunds their cost. Since 2012, the off-label medicines have been mentioned in the list of reimbursed drugs, including the range of their out-of-registration indications which are embraced with the reimbursement. Amongst the off-label drugs accepted by the Ministry of Health for children below 18 are those described in the thesis: carvedilol, ramipril, carbidopa-levodopa, propranolol and enalapril (17).

CONCLUSION

Ordaining and preparing compounded drugs in community pharmacies created the possibility of adjusting the doses of medicinal substances, contained in manufactured medicinal products intended for the adult, to individual needs of the children. The only compounded form ordered by the physicians were divided powders for an internal use. The ordination of any other pediatric form was not observed. Starch capsules for powder preparation provided the only 'package' for the dose of the compounded powder, which after pouring, solving or suspending in water was administered to children. The addition of lactose to the content of the compounded drug may contribute to the growth of photo-stability of the medicinal substance received *via* micronization of a ready medicinal product. Such a shift of the form, between an oral tablet and divided powder for an internal use, did not cause a change in the method of administration. The information on indications and the way of dosage for children, inserted in the Summary of Product Characteristics, enables the administration which follows the registered indications, despite the shortage of an appropriate dose in the pharmaceutical market. In contrast, an absence of the information regarding the indications and a

dosage for children in the Summary of Product Characteristic, results in an off-label administration, in case of a child.

REFERENCES

1. Madanecka A., Sznitowska M.: Forum Medycyny Rodzinnej 3, 6 (2009) (Polish).
2. Dzioba Ł., Stańczak A.: Acta Pol. Pharm. Drug Res. 69, 341 (2012).
3. European Commission Directive 2001/83/EC, 6th November 2001.
4. European Comission Guideline on Summary of Product Characteristics. Revision 2, (2009).
5. Brion F., Nunn AJ., Rieutord A.: Acta Paediatr., 92, 486 (2003).
6. Helin-Tanninen M.: http://epublications.uef.fi/pub/urn_nbn_fi_uef-20100060/urn_ nbn_fi_uef-20100060.pdf
7. Ghulam A., Keen K., Tulen K., Chi-Kei Wong I., Long P.F.: Ann. Pharmacother., 41, 857 (2007).
8. Muśko M., Sznitowska M.: Acta Pol. Pharm. Drug Res. 70, 137 (2013).
9. Sosnowska K., Winnicka K., Czajkowska-Kośnik A.: Acta Pol. Pharm. Drug Res. 66, 321 (2009)
10. Teixeira de Barros C.M., Almeida A.J.: EJHP Practice, 14, 26 (2008).
11. Jamrógiewicz M., Jasińska K., Sawicki W.: Farm. Pol. 68, 858 (2012) (Polish).
12. Kanturski J., Prokuratura i Prawo, 10, 94 (2012) (Polish).
13. Chalumeau M., Treluyer J.M., Salanave B., Assathiany R., Cheron G., Crocheton N. et al.: Arch. Dis. Child. 83, 502 (2000).
14. Carvalho C.G., Ribeiro M.R., Bonilha M.M., Fernandez Jr. M., Procianoy R.S., Silveira R.C.: Journal of Pediatria, 88, 6 (2012).
15. Khdour M.R., Hallak H.O., Shab'an K.A.A., AlShahed Q.N., Hawwa A.F., McElnay J.C; Int. J. Clin. Pharm. 33, 650 (2011).
16. Zajdel J.: Przegl. Lek. 68, 33 (2011) (Polish).
17. Reimbursement list (2012):_http://www2.mz.gov.pl/wwwmz/index?mr=m111111&ms=&ml=pl&mi=&mx=0&mt=&my=0&ma=031339

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