



# REDUCING PAEDIATRIC OFF-LABEL-USE BY IMPROVING DRUG INFORMATION – COMPARISON OF MEDICINES APPROVED FOR USE IN CHILDREN AND A DATABASE FOR CHILDREN'S MEDICINES

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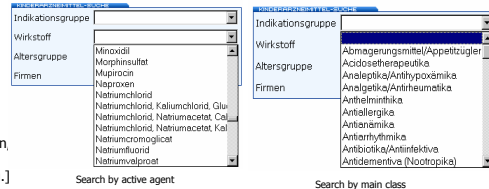


## Motivation

For the first time in Germany a database for physicians and pharmacists providing information on pharmaceutical agents licensed for use in children is available.

In our survey we investigated whether the database complies with requirements necessary to reduce off-label-use in paediatrics. We performed an analysis on the integrity of the database with regard to active agents, formulations, group specificities and age limitations.

- 46% of children's prescriptions are not in accordance with approval [1]
- Serious adverse events occur three times more frequently in off-label prescriptions [Knöppel et al]
- 20% of all marketed drugs are considered licensed for use in children [H. Seyberth (pers.)]
- Drugs not licensed for use in children are prescribed despite of approved alternatives [Hulpe-Wette, Ärztezg.]



## Reducing paediatric Off-Label-Use

**Table 1: Target-performance comparison**

Availability according to Rote Liste Online (drug information for Germany, 05.12.2006)	Search criteria	Availability according to database (05.12.2006)
0,025% Xylometazoline nose drops	Xylometazoline baby	not available
75mg Acetaminophen suppositories (3 kg body weight)	acetaminophen newborn	not available
0,25 mg Sodium fluoride tablets	Sodium fluoride newborn	not available
85% Glycerol suppositories	laxative baby	not available
Breathe balm (chest rub)	antitussive External use	not available

We compared results obtained in search of the five criteria (table 1) in both the database and 'Rote Liste' (red list, drug information for Germany) for licensed use in children. An antitussive, a rhinologic agent and an analgesic were chosen because of the frequent prescription by German physicians in 2006. For reasons of representativeness we also included a dental pharmaceutical and a remedy for diarrhoea. Twice we entered the main class; three times we selected an active agent

Example: The extensive search for a drug for newborns with Acetaminophen does not retrieve any results. The smallest available formulation according to the database is a 125 mg dosage form for babies. However 75 mg suppositories without an age limit are accessible in Germany.

## Products without age restriction

Only three out of 19 drugs without an age limit, are available in the database:

- Somatropin
  - Permethrin
  - Impenem/Cilastatin
- But their limitations according to the database are:
- newborn
  - toddler
  - newborn



## Approvals of children's medicines since 2001 and presence in database

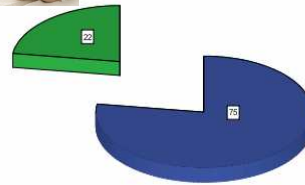
Subsequently we extracted 97 pharmaceuticals for children from a list of 113 medicines licensed for use in children between 2001 and 2006 [www.vfa.de]. We excluded devices for application and agents occurring over again. 22 active agents could be chosen in the database search screen, a total of 75 pharmaceuticals could not be selected.

Further research revealed: Approximately 10 700 medicines are licensed for use in children in Germany. The database contains 974 SPCs. Only 10 - 30 % drugs approved for use in children are covered by the database.



Quality assuring drug monographs for inscriptions are not listed. Foreign drugs licensed abroad and importable by German pharmacists are also not included in the database. Both would round out the database.

presence in database  
■ not available  
■ available



## Premature infants

Number	Group	Age
-	no age limit	No restriction
-	Pre-term infants	< 36th week of gestation
1	Newborn	till 27th day
2	Baby	28 days till 11 months
3	Toddler	12 till 23 months
4	Preschooler	2 till 5 years
5	Pupil	6 till 11 years
6	Adolescent	> 12 years

Fig.1: age groups

main class	active agent	age	company
			1-Neugeborene (bis 27 Tage)
			2-Säuglinge (28 Tage bis 11 Monate)
			3-Kleinkinder (12 bis 23 Monate)
			4-Vorschulkinder (2 bis 5 Jahre)
			5-Schulkinder (6 bis 11 Jahre)
			6-Jugendliche (ab 12 Jahre)

Fig.2 : database for approved children's medicines

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For age classification in children (see numbers 1 to 6 Fig.1) associated in the literature [2] seven groups were matched by the European agency. The database (see Fig. 2) for medicines approved for use in children lacks two groups

- 'pre-term infants' and
- 'no age limit'.

Two drugs,

- Ibuprofen and
- Pavilizumab



out of 97 listed pharmaceutical agents, licensed for use in children are approved to treat pre-term infants. According to the database Ibuprofen and Pavilizumab are available not before 28 days resp. term birth. The Ibuprofen succus is licensed for the treatment of

- pain,
- fever and
- inflammation,

whereas the Ibuprofen injection solution for pre-term infants is licensed for the treatment of haemodynamic patent ducti arteriosus (orphan drug status).

## Database for approved children's medicines – Orphan Drugs

### Orphan drug status \* presence in database crosstabulation

Quantity	presence in database		total
	not available	available	
Orphan drug non- orphan drug status orphan drug	63	20	83
total	12	2	14
	75	22	97

A total of 14 drugs out of 97 products, extracted from a list of pharmaceuticals approved for use in children are granted the orphan drug status by the European agency.

The database provides information on only two orphan drugs licensed for use in children. 12 orphan drugs cannot be selected in the active agent search window.

### References

- [1] Conroy et al. BMJ 2000 ;320:79-82.  
[2] EMEA (1999) ICH Topic E 11. <http://www.eudra.org/emea.html>

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Absent in database: approved active agents (orphan drugs) for use in children (status 08.12.2006)

Abacavir + Lamivudin, Adrenalin,  $\alpha$ -Galactosidase, Anagrelid, Artemether + Lumefantrin, Atomoxetin, Atovaquon + Proguanil, Bosentan, Busulfan, Calcium folinate, Carglumic acid, Cefepime, Cholera-Vaccine, Clofarabine, Darbepoetin  $\alpha$ , Deferasirox, Desloratadine, DT-Pertussis-Polio-vaccine, Emtricitabine, Enfuvirtide, Epinastine, Ertapenem, Etoricoxib, Fexofenadine, Fluticason propionate, Formoterol + Beclomethasone, early summer Meningoencephalitis-vaccine, Galsulfase, Hepatitis-A&B-vaccine, Hepatitis-A-Typhus-vaccine, Hepatitis-B-vaccine, HPV-vaccine, Imatinib, Immunglobuline G, Insulin glargine, Insulin aspart, Insulin detemir, Interferon  $\gamma$ -1b, Interferon  $\alpha$ -2b, Larondase, Levetiracetam, Levobupivacaine, Levocetirizine, Lopinavir + Ritonavir, Macrogol 3350 + NaCl + NaHCO<sub>3</sub> + KCl, meningococcal-vaccine, Methotrexat, Miltefosin, MMRV-vaccine, Metopason fuorat, Montelukast, Nadifloxacin, Nitisoinon, Nonafact, Octocog  $\alpha$ , Olopatadin, Omalizumab, Orlistate, Oseltamivir, Oxycodone & Naloxone, ropacloprid fraction of cow lung, Pimecrolimus, Piritramide, Pneumococcal-vaccine, Pravastatin, Protein C, Racecadotril, Rasburicase, Rotavirus-vaccine, nitric oxide, Sumatriptane, Telithromycin, Valproic acid, Zanamivir

## Conclusions

The database conveys the impression, that proprietary medicinal products containing particular active agents are not available for certain age groups. If health care professionals, when making a therapeutic decision, only refer to the database as a source for information, incompleteness may cause off-label-decisions. For the database to effectively reduce pediatric off-label-use, notices on the extent of information, a narrative of sources of information, the scientific advisers, data on integrity, the updating period and limits of the database are indispensable.