Comments (10 October 2007) from Hannsjörg W. Seyberth on behalf of the German Society of Pediatrics and Adolescent Medicine (DGKJ) to the *Provisional First WHO Model List for Children (16 August 2007)*

General impression:

The first draft has already extensively been discussed from a German perspective in our comments from May 31 07. In cases where we have not seen much changes in the present version of the list, we again will refer to these comments.

Our present general impression on the list from 16 August 07 is that this early version of an EML for children under 12 years of age all over the world is still somewhat unbalanced. In part this is influenced by the structure of "adult list", which may have been followed too closely, by the majority of English speaking countries and also by the urgent needs of the developing countries at the expense of the problems in the developed world and.

So we are missing; (a) a separate section dealing with the pharmacotherapeutic needs for sedation in infants and children, (b) a more complete list of antidotes, (c) a separate section dealing with metabolic diseases, (d) a separate paediatric ENT-section, (e) a separate section dealing with the very specific problems of neonates such as pharmacological closure of the ductus arteriosus, management of neonatal respiratory distress, pulmonary hypertension and apnoea etc.. On the other hand the list for MDR-TB, HIV and child-psychiatry (age limit of this list is 12 years) appears to be quite comprehensive.

It is well known that there is some kind of Anglo-Saxon antipathy towards suppositories, which do, however, have a clear cut paediatric indication for example in the management of febrile convulsions (benzodiazepines), acute management of obstructive respiratory diseases in infants and small children (corticosteroids), sedation (e.g. benzodiazepines) or in a vomiting infant with infection or even an older child with migraine or motion sickness (antiemetics). Moreover, codein and chlorephenamine are quite popular in the UK and US without convincing medical reason(s) (see our comments from May 31, 07), while metamizol/dipyrone, which is essential in anaesthesiology and particularly in oncology and palliative care in central Europea, is still missing on the list.

Last but not least in quite a few comments from colleagues there was the expression of concern that we might move too much in the direction of a two class medicine by recommending medicines for developing countries, which would hardly anymore be used in the developed countries because of either high toxicity, low or unproven efficacy or unpractical administration (see below). In addition our colleagues would like to know, how we are going to proceed with the essential needs of pharmacotherapy of the large variety of orphan diseases in paediatrics, such as cystic fibrosis, septic granulomatosis , congenital metabolic diseases or salt losing tubulopathies and endocrinopathies, where quite cost-effective pharmacointerventions are available.

Specific comments:

1. ANAESTHETICS

1.1 General anaesthetics

Halothane should be replaced by sevofluran, which is apparently less hepatoxic and arrhythmogenic (statement from the the Working Group for Child Anaesthestioloy, WHCA)

Ketamine is also needed for rectal, intranasal and oral administration (see also our comments from May 31, 07)

Propofol is worthwhile considering for short surgical procedures (WGCA and other "intensivists").

1.2 Preoperative medication

It is highly desirable to replace diazepam by midazolam as expressed by several experts and societies/working groups (see also our comments from May 31, 07).

Fentanyl (for long-term procedures) and alfentanyl (for short-term procedures) have replaced morphine in our country and probably in other developed countries (WHCA).

1.3 Sedation for short-term procedures including conscious sedation for painless imaging

Ketamine (see above)

Propofol (see above)

Midazolam (see above)

Chloral hydrate suppositories (Sury MRJ et al. in Lancet 1999 and in Clinical Radiology, 2005) This medicine would have to be reintroduced in the EML for Children after it has been deleted from the adult list more recently.

Promethazine is better listed here for children over 2 years instead under antiemtic medicines (see below).

2.1 Non-opioids and NSAIMs

Ibuprofen should not be recommended for the time being for pharmacological closure of the ductus arteriousus in pretem infants. Indomethacin is still the drug of choice for this indication (see WHO Guideline on *Promoting Safety of Medicines for Children* 2007 Annex 2).In addition the possible causal relationship between kernicterus and ibupofen treatment in a term newborn infant could be demonstrated in a more recent case report (Gal P et al. J Pediatr Pharmacol Ther 2006).

Indomethacin should be on the list also for other reasons. As mentioned in the comments from May 31 07 paediatric rheumatologists prefer this NSAIM in autoimmune connective tissue disorders, because of its general high tolerability in children in contrast to adults, the availability of a suspension, its potency as prostaglandin synthesis-inhibitor (for ref. see comments from May 31, 07) and fear of ibuprofen-induced aseptic meningitis (Jolles S et al. Drug Saf 2000; Nguyen HT and Juurlink DN Ann Pharmacother 2004; Rodriguez SC et al. Medicine 2006).

Finally indomethacin is the medicine of choice in the peri- and postnatal management in a group of orphan renal diseases, the life-threatening , congenital salt-losing tubulopathies (Konrad M et al. Pediatrics 1999; Komhoff M et al. Acta Paediatr 2005; see also the EMEA priority list for studies into off-patent paediatric medicinal products: http://www.emea.europa.eu/pdfs/human/peg/19797207en.pdf).

Don't we need ibuprofen suppositories for uncooperative infants and small children with infections and vomiting?

Paracetamol is now available as an intravenous preparation for severe pain and high fever, which can not be treated effectively with oral or rectal administration, however cost might be a limiting factor for this medical product.

Metamizol/dipyrone is a very popular alternative in central Europe, as already explained in the comments from May 31, 07. This strong non-opioid analgesic and antipyretic agent is well accepted and essential in paediatric oncology and palliative care.

2.1 Codein has already been challenged in the comments from May 31, 07. There is actually no need anymore for this opioid as it is without effect in about 10 % of the patient population and it might be dangerous for nursed infants from mothers taking this medicine.

Even as a symptomatic cough suppressant codein is of no real use anymore. There are alternatives with better pathophysiological reasoning such as solbutamol inhalation for exsudative cough or ibuprofen in dry and itching cough often associated with a viral infection of the upper respiratory tract.

Fentanyl and probably alfentanyl were thought to belong on the list. This was the unanimous opinion of experts from several paediatric disciplines such as anaesthesiology, intensive care medicine, oncology and neuropeadiatrics.

3. Anitallergics

Chlorphenamine certainly needs to be reviewd. There are probably better histamine H1-antagonists available.

What about sodium cromoglicate here on the list? It certainly does have a strong antiallergic effect with negligible side effects.

4. ANTIDOTS AND OTHER SUBSTANCES USED IN *INTERNAL AND EXTERNAL* POISONINGS

(see also Annex 3 with the provisional but quite comprehensive comments from the perspective of the Inborn Error of Metabolism Study Group

4.2 Specific antidotes

Although many antidotes (about sixty percent) do not correspond to the demands of licensing (Lifshitz M et al. Eur J Clin Pharmacol 2001), this list needs to be more completed.
We would like to suggest the addition of the following antidotes:
Physiostigmine for anticholiergic poisening as well as atropin and tricyclic antidepressants intoxication.
Methylene blue for methemoglobinemia treatment
Sodium-thiosulfate for cyanide intoxication
Flumazenil for benzodiazepine intoxication

6. ANTI- INFECTIVE MEDICINES

(see Annex 1 with the comprehensive comments from Reinhard Berner on behalf of the German Society for Pediatric Infectious Diseases (DGPI) and Annex 2 with the comments from Michael B. Krawinkel on behalf of the German Association for Tropical Pediatrics (AGTP) with focus on drugs for the treatment of parasite infections.
Only additional comments from other experts and learned societies are mentioned here.

6.2.1 Betalactam medicines

Ceftriaxone: After the warnings from several drug agencies in Europe also the FDA has sent an ALERT last month addressing the interaction of ceftriaxon with calcium-containing products based on fatal cases in neonatology (see: http://www.fda.gov/cder/drug/InfoSheets/HCP/ceftriaxone.htm).
There is certainly a need for an alternative in neonatology (e.g. cefotaxime), particularly when one also considers the potential danger of ceftriaxone-induced kernicterus by protein binding displacement of bilirubin.

6.2.2 Other antibacterials

Azothromycin: is also indicated for infections with mycoplasma pneumonia and not only for trachoma. Has the extreme long half-life of this macrolide been considered, which might lead more easily to the development of bacterial resistance?

6.3 Antifungal medicines

Griseofulvin: This is another example where a medicine oughtto be replaced by better alternatives.Besides fluconazoe and nystatin the following essential antifungal compounds are worthwhile considering even for developing countries with a growing population of immune-compromise patients: voriconazo, caspofungin and itraconazol.

6.4 Antiviral medicines

Gancyclovir is essential for CMV-prophylaxis in CMV-negative patients after transplantation of a kidney from a CMV-positive donor.

7. ANTIMIGRAINE MEDICINES

7.1 For treatment of acute attack

Paracetamol in rectal or intravenous administration might be very helpful in common migraine, which is often attendant with nausea and vomiting (see above). Another alternative could be the co-medication with an effective antiemetic agent such as the histamine H1-antagonist dimenhydrinate as suggested by our neuropaediatric expert. This compound does not have such a prominent sedative effect as promothazine and certainly should be prefered when comparing with metoclorpramide, because of its well known extrapyramidal side effects in children (see our comments from May 31, 07).
Triptanes are not yet cost-effective to be included in this list?

7.2 For prophylaxis

Aspirin (1mg/kg/day) might be an equivalent alternative to propranolol. Particularly when one considers to higher risk of ischemic brain diseases and other ischemic cardiovascular events in patients suffering from migraine with aura (Diener HC et al. Curr Opin Neurol 2007; Winquershuk DM et al. Neurologist 2007; Weinberger J Curr Cardiol Rep 2007 etc.).

8.1 Immunosupressive medicines

Complementary List

Tacrolimus and mycophenolate mofitil (MMF) have been proposed as essential immunosuppressive medicines in the management of paediatric transplantion by our experts of the Working Group of Pediatric Nephrology (APN). When comparing these medicines from the clinical effectiveness and the cost-effectiveness point of view with ciclosporin or azathioprine there are certainly savings in the expenses due to a reduction of hospitalization and treatment courses of acute rejection episodes in the first post-renal transplantation year. Also the long-term use of tacrolimus is a more cost-effective solution in terms of the number of survivors and patients with a functioning graft as compared to microemulsiffied ciclosporine (Orme ME et al. Pharmacoeconomics 2003).

8.3 Hormones and antihormones

Complementary List

Fludrocortisone tabs are essential as a supplementary hormone to replace the mineralocorticoid component of the adrenal gland e.g. in salt-losing patients with congenital adrenal hyperplasia.
Desmopressin (i.v., oral and intranasal administration) for replacement of antidiuretic hormone for congenital and acquired diabetes insipidus.
Contraceptives might become essential for girls entering into puberty with the age of 8 and 12 years.

8.4 Medicines used in palliative care

Metamizol/dipyron ought to be on the list, because of its great advantages such as being much more potent than the usual NSAIMs, has no major CNS-side effects in contrast to the opioids and is available in almost all kinds of formulations. The major concern of its haematological adverse reaction is of negligible relevance in this situation.

10.2 Medicines affecting coagulation

Complementary List

Heparin sodium: Here it should be mentioned that the flushing solution, which is frequently used in newborn infants, should not contain any benzyl alcohol (see WHO guideline Promoting Safety of Medicines for Children).
*Low-molecular-weight heparin (LMWH) ultimately may replace standard unfractionated heparin in the treatment of thrombosis. These agents offer the advantage of fixed-dose subcutaneous administration without monitoring or dose adjustment. Recent trials have shown specific LMWHs to be at least as effective as unfractionated heparin in preventing recurrent thrombosis with a comparable or lower risk of hemorrhages. (*word-for-word-citation from Goodman & Gilman's Textbook of Pharmacology from the year 1996) No further comments from our side.

12. CARDIOVASCULAR MEDICINES

12.2 Antiarrhythmic medicines

Here are some additional suggestions from our colleagues in neonatology and intensive care medicine in addition to those already mentioned in our comments from May 31, 07:
adenosine, amiodarone and flecainide

12.3 Antihypertensive medicine

No additional suggestions to those already made in the comments from May 31, 07.

12.4 Medicines used in heart failure

If septic shock is included then epinephrine, norepinephrine, dobutamine and probably mirinone are candidates for the complementary list, while captopril ought to be on the core list in addition to digoxin and furosemide.

12.5 Antithrombotic and antiplatelet medicines

Aspirin (low dose) ought to be included in this context as already mentioned in our previous comments.

12.6 Lipid-lowering agents

(see Annex 3 with the provisional but quite comprehensive comments from the perspective of the Inborn Error of Metabolic Study Group)

12.7 Medicines for ductal closure

Indomethacin as already mentioned above under 2.1 Non-opioids and NSAIMs.
For the time being this NSAIM remains for this indication the medicine of choice. For further discussion see the WHO guideline *Promoting Safety of Medicine for Children Annex 2.*

13. DERMATOLOGICAL MEDICINES (topical)

13.1 Antifungal medicines

Benzoic acid + salicylic acid is considered as being not anymore needed by our expert of the Network of Interdisciplinary Pediatric dermatology.
Miconazole is also not needed anymore.
Ciclopiroxolamin is highly recommended to be listed because of its combined antimycotic and antibacterial activity.

13.2 Anti-infective medicines

Methylrosanilinium chloride (gentian violtel) is still considered as useful.
Neomycin sulfate + bacitracin is an old-fashioned antibiotic combination with high-resistance levels and should therefore probably be deleted from the list.
Instead of that the following newer compounds are candidates to be listed:
Mupirocin, chlorhexidine and triclosan

17. GASTROINTESTINAL MEDICINES

17.1 Antacids and other antiulcer medicines

Aluminium hydroxide is probably not essential, particularly when one considers the potential of aluminium toxicity.
Magnesium hydroxide is also not essential anymore today.
Omerprazole or another proton pump inhibitor ought to be considered in the list in addition to the less potent H2-receptor antagonist ranitidine. The first one is also essential as co-medication in a variety of conditions such as for eradication of *Helicobacter pylori* or for prevention of NSAIMs-induced ulcers.

17.2 Antiemetic medicines

Metoclopramide should be considered as doubtful for being an essential antiemetic medicine for infants and children because of its extrapyramidal side effects (see above and our comments from May 31) and the availability of better alternatives (see below).
Dimenhydrinate could replace promethazine as an antiemetic medicine, which does have a strong sedative effect. Dimenhydrinate, which is labelled for all paediatric populations except for newborns in Germany, is the medicine of choice for the prevention and treatment of motion sickness and is available in all age appropriated formulations in particular as suppositories, a formulation, that is essential for antiemetic medicines.
Dexamethasone will probably be mentioned in the list of adjuvant medicines used in oncology.
5HT3 antagonists (e.g.ondansetron) are also needed in the management of nausea and vomiting in children receiving cytotoxic medicines and in the treatment of postoperative nausea and vomiting.

17.3 Anti-inflamatory medicines

Why is this sub-section completely deleted? See below under 17.5.2

17.5 Medicines used in diarrhoea

(see **Annex 2** with the comments from Michael B Kravinkel on behalf of the German Association for Tropical Pediatrics with focus on drugs for the treatment of parasite infections and diarrhoea in children)

17.5.2 Medicines for diarrhoea in children

Zinc sulfate has been questioned for being an essential medicine for children by several experts. Aminosalicylates (e.g. sulfasalazine) form together with corticosteroids the basis of pharmacotherapy of chronic bowel disorders (Crohn's disease and ulcerative colitis), conditions, which are almost always associated with severe and chronic diarrhoea.

24.4 Medicines used for obsessive compulsive disorders and panic attacks

(see **Annex 4 with** the suggestion and argumentation from the German Association of Research-based Pharmaceutical Companies, which would like to see the SSRI fluvoxamine on the essential list.)

25. MEDICINES ACTING ON THE RESPIRATORY TRACT

25.1 Antiasthmatic

Budesonide could be replaced by fluticasone propionate from the point of view of several experts in that field. Besides aerosol also dry powder inhalation and at least one corticosteroid-suppository for the acute management of obstructive respiratory diseases needs to be considered.

Epinephrine (adrenalin) in asthma has been generally superseded by beta2-selective adrenergic receptor agonist (see WHO Model Formulary 2004) and should be replaced for this indication. Salbutamol as a oral of rectal formulation do have a low and unpredictable bioavailability; therefore they can be considered as not essential.

25.2 Other medicines on the respiratory tract

Caffeine citrate has an indication as a respiratory stimulant in neonatal apnoea but certainly not as an antiasthmatic medicine. Theophyline would be an alternative of the methylxanthines. However, in small childen therapeutic drug level monitoring (TDM) is essential as there are enormous pharmacokinetic variations of this medicine with an extremely narrow therapeutic window. Why not considering a leukotriene antagonist such as montelukast, which, however, is still on patent?

27. VITAMINS

(see here also Annex 3 with provisional but quite comprehensive comments from the perspective of the Inborn Error of Metabolism Study Group)

ACKNOWLEDGEMENT

The following colleagues and experts, learned societies, working groups and institutions have contributed to these comments:

- Matthias Schwab for the Committee on Drug Safety in Children of the DGKJ and for the Working Group Pediatric Nephrology (APN)
- Rudolf Korinthenberg for the Committee on Drug Safety in Children of the DGKJ
- Reinhard Berner for the German Society for Pediatric Infectious Disease (DGPI)
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- Andreas Leonhard from the Center of Pediatrics and Adolescent Medicine of the Philipps Universtity in Marburg
- Hea Sook Kim-Berger from the Center of Pediatrics and Adolescent Medicine of the Philipps University in Marburg

ANNEX 1

Additional comments from Reinhard Berner on behalf of the German Society for Pediatric Infectious Disease (DGPI)

6. ANTI-INFECTIVE MEDICINES
6.2 Antibacterials

- amoxicillin + clavulanic acid: the 7 : 1 –formulation is better tolerated and can be applied twice daily
- cefazolin: cefazolin ist also needed for therapy e.g. endocarditis, osteomyelitis due to S. aureus.
- cefuroxim (or cefotiam) as a parenteral cephalosporin (group 2) is lacking
- cefotaxim (as an alternative to ceftriaxone) as a parenteral cephalosporin (group 3a) is lacking e.g. for treatment of meningitis, UTI or abdominal infections
- ceftazidime as a parenteral cephalosporin (group 3b) is necessary for e.g. Pseudomonas-infections, as an alternative cefepim can be listed as a parenteral cephalosporin (group 4) with activity against Pseudomonas (and other nonfermenters)
- all oral cephalosporins are lacking e.g. cefadroxil (oral group 1), cefuroximaxetil (oral group 2), **c**efpodoximproxetil or cefixim (oral group 3)
- cloxacilllin: flucloxacillin is more convenientphenoxymethylpenicillin: benzathin-penicillin V is more convenient (application twice daily)
- piperacillin as a parenteral penicillin with gram-negative activity is lacking
- piperacillin+tazobactam as a parenteral penicillin with gram-negative and anaerobic activity is lacking
- imipenem+cilastatin: meropenem is an important alternative since it can be used in high doses for the effective treatment of bacterial meningitis; as a rule it is better tolerated than imipenem
- ciprofloxacin: the restriction for the use only for Shigella infections is not acceptable: it should also be available for Bacillus anthracis infections, infections by Pseudomonas aeruginosa or other multidrug resistant Gram-negatives (e.g. in cystic fibrosis patients), Typhus and Paratyphus, and for prophylaxis of meningococcal meningitis in developing countries. Furthermore, moxifloxacin should also be approved for use in children.
- doxycycline: age restriction (>9 years) necessary; restriction for use only in Cholera is not acceptable. Important for the treatment of Lyme borreliosis, Mycoplasma infections etc. (no other tetracyclines are necessary)
- erythromycin: there is a risk of pyloric stenosis in neonates; therefore restrictive use in this age group is recommended; other macrolides (e.g. clarithromycin) including erythromycin-estolate and azalides (e.g. azithromycin) should be included for treatment of e.g. respiratory tract infection including Bordetella pertussis and atypical mycobacterial infections. Ketolides (e.g. telithromycin) although not yet approved in children should also be included.
- gentamicin: netilmicin, tobramycin, amikacin should be included for treatment of infections due to resistant gram-negative rods, in particular in cystic fibrosis patients.

In general: Not only adults, but also children suffer from severe and rare infectious diseases and infectious diseases caused by multidrug resistant pathogens, in particular in hospitalized and immunodeficient patients. Children have the same rights as adults to

participate on progress in medicine. Therefore, appropriate alternative drugs are needed which have to be studied and approved in children, e.g. linezolid, daptomycine, tigecycline, quinopristin/dalfopristin, telithromycin.

6.2.4 Antituberculosis medicines

- ethambutol, isoniazid, pyrazinamid are not available as liquids in Germany
- ethionamid is not available in Germany, but prothionamid

6.3 Antifungal medicines

- itraconazol, voriconazol (VFEND), posaconazol (NOXAFIL) are lacking
- echinocandins are lacking
- liposomal amphothericin is lacking;
  all of them are essential drugs for the treatment of e.g. invasive fungal infections such as aspergillosis in neutropenic patients

6.4 Antiviral medicines

- ganciclovir, valgancyclovir, foscarnet are lacking
- cidofovir is lacking
- brivudin is lacking
- zanamivir (RELENZA), oseltamivir (TAMIFLU) are lacking

6.4.2. Antiretroviral medicines

- nelfinavir is no longer on the market, can be eliminated
- ritonavir is only indicated as a booster for PI in the dosage of 2x75mg/m2 or 2x100mg/d and no longer in the antiretroviral dosage
- saquinavir is available as 500mg capsule
- tenofovir, atazanavir and fosamprenavir are lacking but they are used off-label in children

6.5.1 Antiamoebic and antigiardiasis medicines

- diloxanide is not recommended below 25 kg bw – thus, no drug to eliminate Entamoeba histolytica cysts is offered. In published studies from Vietnam paromomycin has been more efficient than diloxanide to eradicate e. histolytica cysts - and thus, paromomycin tablets should be included in the list.
- metronidazole has a low efficacy in eliminating G. lamblia due to compliance problems because it has to be given three times daily for at least 3 better 5 days. In studies tinidazole and ornidazole given once or once a day for two days at 30-70 mg/kg bodyweight has demonstrated higher efficacy and one of them should be included in the list.

ANNEX 2

Comment from Michael R. Krawinkel on behalf of the German Association for Tropical Pediatrics with the focus on drugs for the treatment of parasite infections and diarrhoea in children

Group	Generic	Remark
6.1.2. Antifilarials, Complementary list	diethylcarbamazine	tablets with 20 or 25 mg or a syrup desirable
6.1.3. Antischistosomals and antitrematode medicine	praziquantel	tablets with 250 mg or a syrup desirable
	triclabendazol	tablets with 100 mg or a syrup desirable
6.5.1. Antiamoebic and antigiardiasis medicines	diloxanide	tablets with 100 mg or a syrup desirable;
6.5.3. Antimalarials, 6.5.3.2. for prophylaxis	proguanil	tablets with 50 mg or a syrup desirable
17.5.1. medicines for diarrhoea in children	oral reyhdration	sachets with 45 mmol sodium desirable for children with ordinary viral diarrhoea and children with severe malnutrition
17.5.2. medicines for diarrhoea in children	zinc sulfate	This is not an essential drug.
26.1 solutions correcting water, electrolyte and acid-base disturbances - oral	**new:** electrolyte-mineral-solution for the management of severe childhood malnutrition (acc. to WHO-guidelines) Potassium chloride 89.5 g Tripotassium citrate 32.4 g Magnesium chloride ($MgCl2 \cdot 6H2O$) 30.5 g Zinc acetate 3.3 g Copper sulfate 0.56 g Sodium selenate 10 mg Potassium iodide 5 mg to be diluted with 1000ml water before use; 20 ml to	There is evidence that this solution added to the normal oral rehydration and to the formula used for rehabilitation (e.g. F-75, F-100) reduces the mortality of children with severe complicated malnutrition.

	be added to each feed	

ANNEX 3

Comment on *WHO Model List of Essential Medicines for Children* (EML) from the perspective of the Inborn Error of Metabolism Study Group

("Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen, APS) as part of German Society of Pediatrics and Adolescent Medicine

Inborn errors of metabolism (IEM) are exclusively orphan diseases (prevalence <5:10 000). All patients affected by IEM as a group however represent a considerable proportion of the paediatric population. For example more than 50 000 patients with IEM in the EU may potentially benefit from the nine corresponding drugs approved under European orphan medicinal product legislation since 2001(Drugs for complementary list: 1b-f; 2a-d)[1]. Many of those IEM are potentially life-threatening and disabling. Thus next to ethical and medical responsibility there should also be a strong economic interest of the society to provide essential medicine for these patients.

Drugs for the core list

1. Lipid lowering drugs for familial and secondary hyperlipidaemia

1a) Colestyramine und Colestipol

Both drugs represent current first choice treatment in paediatric patients with hyperlipidaemia, however the evidence is not satisfactory[2].

1b) HMG-CoA-Reductase-Inhibitors (Statins)

So far these efficacious drugs are not recommended before puberty, because of insufficient safety data. However some larger studies recently evaluated by the *US Preventive Services Task Force*[3] indicate that statins may play an important role in paediatric patients in the future. The following drugs have been evaluated positively by this expert group: Lovastatin 10 to 40 mg/d[4-6], Simvastatin 10 mg/d titrated to 40 mg/d[7], Pravastatin 5-20 mg/d[8,9], Atorvastatin 10 mg/d[10]. However overall long term data is still insufficient to anticipate long term effects (one study with Pravastatin over 2 years[9], all others < 1year).

2. Tetrahydrobiopterin (BH_4)

BH_4 so far is only approved as diagnostic compound however it will be approved for the treatment of BH_4 responsive phenylketonuria (PKU) soon. PKU is one of the most common IEM and about 70% of all patients can be expected to be responders[11-16].

3. Drugs for detoxification in metabolic crises

Hyperammonaemia can occur in some IEM (e.g. urea cycle defects, organic acidurias, HHH syndrome) or secondary to liver disease. They can be life threatening so acute therapy should be started before the patient reaches a specialised metabolic unit. Thus those drugs should be on the core list.

3a) Sodium Benzoate

Sodium Benzoate is next to the very toxic sodium phenylacetate, the only intravenously applicable compound to improve nitrogen excretion. But it is only available as a chemical compound (Sigma, Merck). An intravenous formulation of sodium phenylbutyrate which is approved for oral application (Ammonaps®) is expected for some time but sill not on market.

3b) Carnitine/ Levocarnitine

Carnitine as well is needed for detoxification in acute metabolic crises that can be caused by some IEM (e.g. in urea cycle defects, organic acidurias, other amino acid

disorders). Furthermore it is used for substitutive therapy in primary or secondary carnitine deficiency. **Drugs for the complementary list**

Treatment with the following drugs will primarily take place in metabolic units as particular diagnostic facilities and specialists are needed for the management of the corresponding diseases.

1. ENZYME REPLACEMENT THERAPIES

1a) Cerezyme® (Imiglucerase) for Gaucher disease

1b) Fabrazyme® (Agalsidase beta) for Fabry disease

1c) Replagal® (Agalsidase alfa) for Morbus disease

1d) Aldurazyme® (Laronidase) for Mucopolysaccharidose Type 1

1e) Naglazyme® (Galsulfase) for Mucopolysaccharidose Type 6

1f) Myozyme® (Alglucoidase) for Pompe disease

2. OTHER DRUGS

2.a) Carbaglu® (N-Carbamoyl-L-Glu)
enzyme activation in N-acetylglutamate synthase deficiency (NAGS)

2b) Zevesca® (Miglustat)
substrate inhibition for Gaucher disease Type 1

2c) Wilzin® (Zinc Acetate-Dihydrate)
complexation in Wilson disease

2d) Orfadin® (Nitisinone)
enzyme inhibition in Hypertyrosinaemia Type 1

2e) Ammonaps® (Sodium Phenylbutyrate)
conjugation of substrate precursors in urea cycle defects

2f) Cystadane® (Betaine)
cofactor substitution in cystathionine beta synthase deficiency, 6,30-methylen-tetrahydrofolate reductase deficiency and errors of cobalamine metabolism

2g) L-Argininhydrochloride®
substitutive therapy in urea cycle deficiencies and organic acidurias

Additionally **vitamins** (adenosylcobalmine, cobalamine, ascorbic acid, biotine, pantothenic acid, pyridoxal phosphate, riboflavin, tetrahydrofolate), **amino acids** (L-arginine, L-citrulline, glycine, L-lysine, L-methionine, L-proline, thiamine, L-valine) and few other compounds (ubichinone, cholin citrate, sodium citrate, maltodextrine) that may be considered dietary supplements and are needed for the treatment of IEM. **As dietary supplements the may not be in the primary focus of EML and yet it has to be clearly pointed out, that in IEM they are needed not only to prevent nutrient deficiencies but moreover to improve metabolic fluxes that are abnormally decreased by the underlying enzyme deficiency.**

The reference list can be requested from Florian Lagler (florian.lagler@i-med.ac.at)

ANNEX 4

Comments from the German Association of Research-based Pharmaceutical Companies via Siegfried Throm and Thorsten Ruppert:

Fluvoxamine (brand names Luvox®, Faverin®, Fevarin® and Dumyrox®) is an antidepressant which functions pharmacologically as a selective serotonin reuptake inhibitor. Though it is in the same class as other SSRI drugs, it is most often used to treat obsessive-compulsive disorder. Fluvoxamine is widely prescribed to treat depression, and anxiety disorders such as Obsessive-Compulsive Disorder (OCD), Obsessive-Compulsive Spectrum Disorder, Panic Disorder, Social Phobia, and Post-Traumatic Stress Disorder. Fluvoxamine is also indicated for children and adolescents with OCD. Fluvoxamine was one of the first of the SSRI antidepressants to be launched (1984 - Switzerland) and was developed by Solvay Pharmaceuticals. It has been in use in clinical practice since 1983 and has a clinical trial database comprised of approximately 35,000 patients. It was launched in the US in December 1994 and in Japan in June 1999. As of the end of 1995, more than 10 million patients worldwide have been treated with fluvoxamine. Furthermore Fluvoxamine was the first SSRI to be registered for the treatment of Obsessive Compulsive Disorder in children by FDA in 1997. To this regard we would like to suggest to include Fluvoxamine in the WHO Model List of Essential Medicines for Children.