Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Phenytoin

UK/W/065/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	27th July 2015

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section X
INN (or common name) of the active substance(s):	Phenytoin, phenytoin sodium
MAHs:	See section X
Pharmaco-therapeutic group (ATC Code):	N03AB02
Pharmaceutical form(s) and strength(s):	MAH1:100 mg tablet, solution for injection 50mg/ml MAH2: 25mg tablets MAH3: solution for injection 100mg/2ml, 250mg/5ml, capsules 25mg, 50mg, 100mg, hard capsules 300mg, 100mg, 50mg, 25mg, oral suspension 125mg/5ml, 30mg/5ml, chewable tablets 50mg MAH4: 100mg film-coated tablet

I. EXECUTIVE SUMMARY

In May 2013, four marketing authorisation holders (MAHs) submitted paediatric data for Phenytoin, in accordance with an Article 45 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use. The UK is the Rapporteur for this procedure. The MAHs in this report will be designated as MAH1, MAH2, MAH3 and MAH4.

Phenytoin is an anticonvulsant drug that was introduced into clinical practice in 1938 and is widely used worldwide. It is available in four formulations: tablet, suspension, capsule, and parenteral solution.

Phenytoin tablets, oral suspension, and capsules are indicated for oral use for the control of generalised tonic-clonic (grand mal) and partial seizures, as well as the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. Phenytoin orally is also indicated for the treatment of trigeminal neuralgia as second line therapy if carbamazepine is ineffective or patients are intolerant to carbamazepine.
Phenytoin administered as a parenteral solution is indicated for the control of status epilepticus of the tonic-clonic (grand mal) type, as well as the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury. It is also indicated in the treatment of cardiac arrhythmias where first line therapy is not effective.

The MAHs stated that the submitted paediatric studies do not influence the benefit:risk for phenytoin and therefore no consequential regulatory action is needed.

The rapporteur identified some issues that could warrant updates in the current SmPC of phenytoin. In addition, the MAHs were requested to review their safety data and the published literature and decide whether there are any clinically relevant differences between the safety profile of phenytoin between the adult and paediatric populations and if needed, propose SmPC updates.

II. RECOMMENDATION

The rapporteur reviewed the data submitted by the MAHs (original submission and supplementary data after day 89) as well as other relevant literature reports. It is concluded that the paediatric use of phenytoin is well established in the management of seizures and overall the drug's benefit:risk has not changed following this procedure.
However, the rapporteur concludes that the SmPC of phenytoin should be updated to include the following:

- A warning that phenytoin may precipitate or aggravate absence and myoclonic seizures
- A statement about the safety profile of phenytoin in children compared to adults reflecting the different incidence of gingival hyperplasia.

Summary of outcome

☐ No change

☒ Change

☐ New study data

☒ New safety information: sections 4.4, 4.8

☐ Paediatric information clarified

☐ New indication

SmPC changes proposed by the rapporteur:

Section 4.4 Special warnings and precautions for use

PHT may precipitate or aggravate absence seizures and myoclonic seizures.

Section 4.8 Undesirable effects

Paediatric population

The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

III. INTRODUCTION

Four MAHs submitted completed paediatric studies for phenytoin, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

The following documentation has been included as per the procedural guidance:

- All data, including published information, quality, nonclinical and clinical relevant for the paediatric assessment as included in the line listing;
- A short critical expert overview clarifying the context of the data and relevance for the European Union situation;
- A Summary of Product Characteristics/Package Leaflet proposal or justification that changes are not necessary;
- Relevant Periodic Safety Update Report (PSUR) data or reference to PSURs already submitted;

Data were also submitted for fosphenytoin. Fosphenytoin is a phosphate ester pro-drug of phenytoin for IV or IM administration and is indicated in children over 5 years of age. Data have been submitted in accordance with Article 45 for fosphenytoin under a separate procedure from phenytoin and therefore this drug will not be further discussed as part of this work sharing procedure.

IV. SCIENTIFIC DISCUSSION

Phenytoin (PHT) is an anticonvulsant drug of the hydantoin class that is structurally related to the barbiturates. PHT was introduced into clinical practice for the treatment of focal seizures and "grand mal" epilepsy in 1938 and is still a very widely used antiepileptic drug. Initially only an oral form of PHT was available. The parenteral formulation was developed in 1950 for use in convulsions during and after neurosurgery.
PHT decreases seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses.

Seizures and Epilepsy

An epileptic seizure is defined as the clinical manifestation of abnormal or excessive discharge of neurons in the brain (Fisher RS, 2005, Salpekar J, 2013). Epilepsy is a chronic neurological condition characterised by recurrent epileptic seizures. Under the current ILAE (International League against Epilepsy) definition two or more unprovoked seizures would constitute epilepsy. Acute symptomatic seizures (such as febrile seizures or after head trauma) would not lead to a diagnosis of epilepsy. Epilepsy is a global problem affecting some 50 million people worldwide, 85% of whom live in developing countries (Ngugi AK, 2010, WHO epilepsy facts). Epilepsy imposes enormous physical, psychological, social and economic burdens on individuals, families and countries, especially due to misunderstanding, fear and stigma.
Globally:
• 2 400 000 new cases of epilepsy occur each year and at least 50% of these cases begin in childhood or adolescence
• 70% of people with epilepsy could be seizure-free with treatment
• 80% of people with epilepsy do not receive a proper diagnosis and are not properly treated.

A recent review (Ngugi AK, 2011) estimated the median incidence of epilepsy to be 50.4/100,000/year, while it was 45.0 for high income countries and 81.7 for low- and middle-income countries. The authors stated that the cause of higher incidence in low- and middle income countries is likely to be partly attributed to the higher incidence of head trauma, infections and infestations of the CNS and invasive

bacterial infections. The paediatric studies were associated with higher incidence estimates than those involving all age groups.

Seizures can manifest due to many different causes, i.e. genetic, brain tumours, head trauma, metabolic causes, infectious and inflammatory causes, stroke, CNS malformations and a plethora of syndromes associated with epilepsy. Some risk factors are age dependent. In early childhood, metabolic, cerebral anoxia, infection and developmental abnormalities are significant risk factors. In adolescents, hippocampal sclerosis, vascular malformations and trauma are the main aetiological factors (Bhalla D. et al., 2011).
Although seizures in childhood have many causes, in a large number the cause remains unknown.

In 1981, ILAE developed an international classification of epileptic seizures that divides seizures into 2 major classes: partial-onset seizures and generalized-onset seizures. In 2006, a new proposed classification of seizures was published (Engel J, 2006). The 2 main changes in this classification were (a) the use of focal rather than partial and (b) the proposal that a single seizure in the setting of a predisposition for further seizures should be considered epilepsy. A revised proposal for seizure classification was published by ILAE in 2010 (Berg AT et al) with the following main changes: 1. Neonatal seizures are no longer regarded as a separate entity. 2. The subclassification of absence seizures has been simplified and altered. Myoclonic absence seizures and eyelid myoclonia are recognized. 3. A separate category ‘‘epileptic spasms’’ is added. 4. For focal seizures, the distinction between the different types (e.g., complex partial and simple partial) is eliminated. 5. Myoclonic atonic seizures are recognized. A revised proposal is currently being prepared by ILAE.

The majority of paediatric epilepsies consist of age-dependent epilepsy syndromes whose manifestations are affected by ongoing brain maturation. That is the case for the most frequent paediatric idiopathic partial epilepsies (e.g. benign epilepsy with centrotemporal spikes) and for epilepsy syndromes (e.g. West syndrome/Infantile spasms, Dravet syndrome, Lennox-Gastaut-syndrome, myoclonic-astatic epilepsy and Continuous Slow Waves during Sleep).
Another major difference in paediatric and adult epilepsies is that some syndromes carry a grave prognosis for cognitive outcome due to the impact of epilepsy, the so-called epileptic encephalopathies. Focal non-idiopathic epilepsies in childhood may also have an important impact on cognitive development if not treated early and appropriately. Some age-dependent epilepsy syndromes do not persist in adulthood (e.g. West syndrome or benign epilepsy with centrotemporal spikes).

The antiepileptic drug of choice should completely control seizures without producing adverse effects. Monotherapy is important, because it decreases the likelihood of adverse effects and avoids drug interactions. With the exception of relatively rare electroclinical syndromes where there is a clear “best” treatment, in most children with epilepsy several comparable choices are available. Overall there is a paucity of well-designed, properly conducted, randomized controlled studies to inform “best treatment” of children with epilepsy (Glauser T, 2013).

IV.1 Information on the pharmaceutical formulation used in the clinical studies

No information was submitted regarding the formulations used in the paediatric clinical studies.

Comments:

The MAHs did not submit any formulation data.

Some products contain PHT sodium and some contain PHT as a free acid as the active substance. Changing between a product formulated with the free acid to a product with the sodium salt and vice versa, can lead to a change in PHT serum levels because there is approximately an 8% increase in drug

content with the free acid form.
The SmPC of the brand leader in section 4.2 "Posology and method of administration" under the heading "Phenytoin <brand name> capsules, oral suspension and infatabs"states: "although 100mg of phenytoin sodium is equivalent to 92mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised." The rapporteur is of the view that this warning should be in all SmPCs.

In addition, it has been reported in the literature that changing brands of PHT resulted in changes in seizure control in adults and children (Burkhardt RT et al, 2004). Different factors can affect the bioequivalence of different antiepileptics (AEDs), such as solubility, release characteristics and the excipients included.
A paper by Shaw et al (2010) reviewed bioequivalence issues over generic substitution of AEDs. "Bioequivalent drug products" display comparable bioavailability but this might not translate to therapeutic equivalence, i.e. same clinical effect and safety. In particular for PHT, the non-linear kinetics of the drug mean that small differences in the amount absorbed could result large changes in drug concentrations.
In 2013 the Commission on Human Medicines (CHM) of the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) reviewed spontaneous adverse reactions received and publications that reported potential harm arising from switching of AEDs in patients previously stabilised on a branded product to a generic. Following this review, CHM concluded that reports of loss of seizure control and/or worsening of side effects around the time of switching between products could be explained as chance associations, but a causal role of drug switching could not be ruled out in all cases. The CHM considered the characteristics of AEDs and advised that they should be classified into three categories based on therapeutic index, solubility, and absorption to help prescribers and patients decide whether it was necessary to maintain continuity of supply of a specific manufacturer's product. PHT was classified as a drug of "Category 1", for which doctors are advised to ensure that their patient is maintained on a specific manufacturer's product.

Finally, the Scottish Intercollegiate Guidelines ("Diagnosis and management of epilepsies in children and young people", 2005) state: "With the exception of phenytoin there is no good evidence of significant difference in bioavailability between proprietary and generic AEDs."

The rapporteur considers that in addition to the warning about changing from the salt to the free acid form of PHT, an additional warning regarding the risk of loss of seizure control and/or worsening of side effects when changing from one product to another should be included in the SmPC. In addition, a recommendation to monitor PHT serum levels when changing from one PHT product to another should be included. BNF-C states: "Care is needed when making changes between formulations and plasma PHT concentration monitoring is recommended."
The rapporteur proposes the following wording to be included in section 4.2 of the SmPC:
"There have been reports of loss of seizure control and/or worsening of side effects when switching from one phenytoin product to another. Therefore, switching between different phenytoin products is not recommended. If, however, it is not possible to avoid changing from one phenytoin product to another (i.e. shortage of supply), phenytoin serum levels should be monitored until steady state is reached."

IV.2 Non-clinical aspects

No data regarding non clinical studies were submitted from any of the four MAHs.

Comments:

The MAHs have not provided information on any non-clinical studies.
The rapporteur has not identified any new preclinical data in the literature relevant to the use of PHT in paediatric patients.

IV.3 Clinical aspects

1. Clinical overview

a. Pharmacokinetics

Four MAH sponsored clinical studies (MAH3), which included children, were conducted to evaluate the pharmacokinetics (PK) and/or bioavailability of different phenytoin formulations.

1. Study a., a Clinical Pharmacology Trial to Compare Half-Strength -PHT suspension, PHT extended capsules , and PHT tablets

This was a single-dose, open-label, controlled, 3-way crossover study that aimed to compare blood levels after the single oral administration of different phenytoin formulations. Ten healthy children were enrolled and divided into 2 groups of 5 each based on age: ≤ 3 years (Group I) and 8 to 12 years (Group II). 9 children completed the study. The median age of the younger group was 3 years and 8 months and 10 years and 3 months of the older group.
The children received a single equivalent dose 10mg/kg of each of the 3 preparations of PHT (suspension, extended capsules, and tablets in a crossover fashion with a minimum of 1 week washout between treatments. The study was divided into 3 phases. In each phase, each child received a single dose of 10mg/kg of the specified PHT preparation under fasting condition. Safety assessments included clinical laboratory tests, physical exams and adverse events monitoring. Blood samples were collected predose, and at 1, 2, 4, 6, 8, and 12 hours postdose of each treatment. Phenytoin blood levels were measured using a colorimetric technique.
Results: Due to weight ranges and dose schedule, the most precise dosing was accomplished with the suspension form since it was measured and administered in increments of 18 mg, whereas the tablets and the capsules could only be administered in increments of 25 and 50 mg, respectively.
All 3 forms of the drug were well tolerated and no significant side effects were reported. One child dropped out from the study at the beginning of Period 2 because of a rash that had developed after the Period 1 dose. There was no statistically significant difference in the blood levels between the two age groups. The phenytoin levels in the younger age group tended to fall off slightly more rapidly than did those in the older age groups. There was relatively no difference in the levels at the first hour after dosing. However, by the end of the second hour, the suspension provided higher blood levels than the other two forms. This higher level was sustained throughout the 12-hour period for the suspension form.

2. Study b., a Clinical Pharmacology Study of PHT suspension, PHT extended capsules, and PHT tablets

This was a multiple-dose, open-label, controlled crossover study which aimed to determine the feasibility of 5 mg/kg/day in children to produce blood levels in the therapeutic range.
Ten healthy children (the same as in protocol 73-21) were selected and divided into 2 groups based on age, with those aged ≤ 3 years being in Group I and those being aged 8 to 12 years being in Group II. 9 children completed the study.
Eligible children received 2-week equivalent doses of PHT at 5 mg/kg/day divided into 2 daily doses of the 3 preparations of PHT suspension, extended capsules, and tablets in a crossover fashion with a

minimum of 1-week washout between each formulation treatment. Dosages of the 3 preparations were computed to the nearest 0.5 mg.
Safety assessments included clinical laboratory tests, physical exams, and adverse events monitoring.
Blood samples were collected prior to the morning medication on Days 1, 2, 5, 8, 11, and 15 (no medication was given on Day 15), at 2 hours after the morning medication on Days 1, 2, 5, 8 and 11, and at 6 hours after the morning medication on Days 1 and 8 in each treatment period. Phenytoin blood levels were measured using a colorimetric technique.
Results: All three forms of the drug were well tolerated and no significant adverse events were reported.
There was no significant difference in the blood levels between subjects in the two age groups. The suspension form appeared to give a higher initial blood level than either the extended capsules or the tablet form. However, this difference was not evident beyond Day 2. The dose of 5 mg/kg/day did not produce blood levels within the toxic range. The investigators considered that the dose administered in this study was therapeutic.

3. Study c., a Clinical Pharmacology Trial to Compare Half-Strength PHT suspension, PHT extended capsules, and PHT tablets

This was a single-dose, open-label, controlled, 3-way crossover study which aimed to compare blood levels after the single oral administration of 10 mg/kg PHT half-strength suspension, PHT extended capsules, or PHT tablets.
Twelve healthy children (aged 2 to 12 years) received a single equivalent dose of each of the 3 preparations. 9 children completed the study. Children aged from 6 years and 6 months to 10 years and 2 months were enrolled. Each phase of the trial was conducted similarly with a minimum of 1-week washout between phases. Safety assessments included clinical laboratory tests, physical exams and adverse events monitoring. Blood samples for drug assay were drawn prior to medication on Day 1 and at 2, 4, 7, 24, and 48 hours post-medication in each phase.
Results: There were no adverse reactions or laboratory abnormalities reported during the trial. Phenytoin suspension formulation was absorbed faster and had a higher peak blood level than either the tablets or the extended capsule formulation. Group mean peak concentrations of 7.7, 6.6, and 6.2 μg/mL occurred at 7, 7, and 4 hours postdose, respectively, for PHT suspension, tablet and extended capsule formulations.

4. Study d., an Efficacy and Clinical Pharmacology Study of Intramuscular PHT (Hydro-alcoholic Diluent) in the Management of Seizure Disorders

This was an open-label, multiple-dose crossover study which aimed to determine whether intramuscularly (IM) administered PHT is as effective as the oral capsule form in the management of seizure disorders by comparing seizure control and drug levels in the blood and urine fol1owing each route of administration.
Participants selected had seizure disorders that required maintenance PHT for seizure control. They should have been receiving PHT for at least 6 months and at a stable dose for at least 3 months prior to study initiation. Patients were excluded for any of the following reasons: chronic liver or renal disease, if they had less than 90% seizure control or any signs of acute phenytoin toxicity such as nystagmus, ataxia, or dysarthria.
Each patient continued on his/her oral formulation divided 3 times daily (TID) for 3 weeks (Phase I) followed by parenteral formulation at the same dose given TID for 3 weeks (Phase II), followed by a final 3-week period (Phase III) using the original oral dose.
Due to the drops in plasma and urine drug levels observed in the initial 7 patients after crossover to the IM administration, an addendum was added to the protocol. In the addendum, 4 patients were selected to compensate for the changes observed. These patients were to be switched to an IM injection of a dose 1.5 times the oral daily dose for 6 to 10 days after establishing steady plasma phenytoin values on oral therapy and then switched back to an oral dose of phenytoin at half-dose of the original oral administration. This amount was to be continued for a period of time equal to the time the patients received IM treatment.

Tolerance was assessed by observation for signs of local irritation. In addition, neurologic examinations for ataxia, nystagmus, dysarthria, and mental confusion were to be performed at the same time that blood specimens were obtained.
Plasma and urine specimens for phenytoin levels were collected from all subjects. Urine samples were collected for 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH), the principal metabolite of phenytoin.

Results: Seven patients participated in the initial trial and 4 patients participated in the trial addendum.
All patients were adults with the exception of a 13 years old child. The child participated in the initial trial and re-entered the trial addendum.
All patients showed local irritation at the sites of injection, with the more severe local reactions occurring during the trial addendum where the dose was highest (1.5 times the original dose). Drug-attributable reactions for PHT (nystagmus and ataxia) were reported in 2 participants and occurred during the IM injection (high dose) in the trial addendum.
Following oral administration, the observed plasma PHT levels were approximately 10 μg/mL for all subjects, including the paediatric subject, as their stabilized fixed doses ranged from 3.95 to 6.45 mg/kg/day. Plasma PHT levels for the IM route (Phase II) were significantly lower (dropped to approximately 60%) than the oral levels in Phase I and the levels during Phase III (oral) were significantly higher than those in both Phase I (oral) and Phase II (IM). A similar trend was noted in the urinary HPPH levels, but the differences were not statistically significant. There was also some evidence to suggest that the seizure control was not as good during Phase II (IM), as 2 of the 7 patients had seizures during this period but not during Phase I or III (oral).
In the trial addendum (adjusted dose), generally the levels remained unchanged during IM administration as compared to oral dosing. The previously described rebound phenomena did not occur. However, the number of patients was very low to establish a trend for the plasma and urine levels during the trial addendum. No apparent exposure differences were observed between the paediatric patient and the rest of the patients (adults) in both the initial and addendum trials.

Comments:

MAH3 conducted three studies examining the clinical pharmacology/blood levels of different PHT formulations in children aged 2-12 years of age. Two studies were conducted in the same cohort of children.
In study a. the investigators reported that by the end of the second hour, the suspension provided higher blood levels than the other 2 formulations (capsules and tablets). However, the MAH also states that although it was intended to dose all children with 10mg/kg, not all received the same dose, depending on the closest increments delivered by the specific formulation. However, "the most precise dosing was accomplished with the suspension". It might be the case that children on the suspension received higher doses and therefore achieved higher blood levels. In addition, the oral suspension and infatabs contain PHT, whereas the capsules contain phenytoin sodium and are also extended release, which might be additional reasons for the differences observed in blood levels. Finally, there may be wide inter-individual variability with equivalent dosages that could account for the identified differences in PHT levels.

In two of the studies, children were dosed with 10mg/kg once daily and in the other (Note: in one study dose is not mentioned) with 5mg/kg/day divided in two doses. The currently approved oral paediatric dose is 5 mg/kg/day (maintenance daily dosage 4-8 mg/kg) and it is recommended that is given in two or three equally divided doses.
Interestingly three of the MAH-sponsored PK studies were performed in healthy children. These studies are old, performed in the 1960s and probably would not be considered ethically acceptable nowadays. The EU document "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population" (2008) states: "Studies such as pharmacokinetic studies, which cannot be performed in adults, should be done in the intended population as far as possible, i.e., the one affected by the disease, although it is recognised that data obtained in affected children may have increased variability."

In one study PHT was administered intramuscularly (IM) in adults and in one child (13 years old) who already had good seizure control on oral PHT. Absorption via the IM route was highly erratic, plasma PHT levels were significantly lower and seizure control was not as good as before. The investigators had to adjust the dose administered via the IM route to achieve comparable levels of PHT but no recommendation regarding the posology for the IM route could be established as there were too few patients (n=4). Moreover, this study only included one paediatric patient and therefore is not informative for the paediatric population.
According to the information included in the SmPC of the brand leader solution for injection, the IV administration is preferred over the IM and the IM administration is not recommended for the treatment of status epilepticus:

"When short-term intramuscular administration is necessary for a patient previously stabilised orally, compensating dosage adjustments are essential to maintain therapeutic serum levels. An intramuscular dose 50% greater than the oral dose is necessary to maintain these levels. When returned to oral administration, the dose should be reduced by 50% of the original oral dose, for the same period of time the patient received phenytoin<brand name> intramuscularly, to prevent excessive serum levels due to continued release from intramuscular tissue sites. If the patient requires more than a week of IM phenytoin, alternative routes should be explored, such as gastric intubation."
And:
"The intravenous route of administration is preferred" and "Intramuscular administration should not be used in the treatment of status epilepticus because the attainment of peak plasma levels may require up to 24 hours."

Three MAHs submitted pharmacokinetic studies (literature articles) relevant to the paediatric population. The pharmacokinetics of PHT in paediatric patients have been reported extensively in the literature, mainly by collecting trough and sparse samples during therapy, in retrospective analyses of drug exposure data collected during therapeutic drug monitoring and in review articles. It should be noted that there was a variety of analytical techniques used for quantitation of PHT levels depending on when these studies were conducted. Furthermore, in most cases, only total PHT levels were reported.

MAH1:

1. Fritsch G. et al, Bioverfügbarkeit von Diphenylhydantoin – Freie Säure – Serumspiegeluntersuchungen eines Präparates mit Laktose als Tablettenbasis (Bioavailability of diphenylhydantoin free-acid serum level determinations using a lactose-based tablet preparation). Monatsschr. Kinderheilkd. (Paediatrics Monthly) 128 (1980), 648-650

Phenytoin serum levels were determined in 103 children during the steady state of phenytoin therapy using a radio-immuno-assay; 94% of the patients had been treated as outpatients, 54% received phenytoin in combination with other antiepileptic drugs. The preparation used was phenytoin as free acid in lactose tablets . A therapeutic serum level of 10-20 µg/ml was reached by a daily oral intake of 6.1 ± 1.6 mg/kg; 27 children had plasma levels above 20 µg/ml, their oral dose was 7.1 ± 1.8 mg/kg/d. Most of these children showed clinical signs of overdosing. The author regarded bioavailability of phenytoin preparations as not only dependent on the type of the substance used (salt, free acid), but also on the excipients used for the preparation of tablets. The author considered that for dosage recommendations, the preparations used are to be taken into account and monitoring of serum levels is considered essential both during therapy initiation and for regular supervision during continued administration of the drug.

MAH2:

1. Bartoszek M et al, Prednisolone and methylprednisolone kinetics in children receiving anticonvulsant therapy, Clin Pharmacol Ther. 1987 Oct;42(4):424-32

Prednisolone and methylprednisolone pharmacokinetic parameters were evaluated in asthmatic children receiving concomitant anticonvulsant therapy. On separate study days, 15 children receiving phenobarbital, carbamazepine, phenytoin, or combination anticonvulsant therapy were administered an intravenous dose of prednisolone or methylprednisolone and compared with a paediatric population not receiving anticonvulsant therapy. Bioavailability of prednisolone after the oral administration of prednisone and methylprednisolone ranged from 86% to 104% during anticonvulsant therapy. Three individuals re-evaluated 13 to 20 days after discontinuing anticonvulsant therapy demonstrated pharmacokinetic parameters similar to those of the control group. Limited studies performed in patients receiving combination anticonvulsant therapy did not demonstrate an additive effect on prednisolone elimination. The authors concluded that differences in the degree of enhancement of prednisolone and methylprednisolone disposition in all three anticonvulsant study groups suggest that different metabolic pathways may be involved.

2. de Wolff FA. et al, Serum concentrations and enzyme induction in epileptic children treated with phenytoin and valproate, Neuropediatrics. 1982 Feb;13(1):10-3

In a group of 59 epileptic children treated with phenytoin (PHT) and valproate sodium (VPA), either alone or in combination, the following effects were studied: (1) the reciprocal effect on the serum levels of the two drugs, and (2) the enzyme-inducing effects of both drugs. VPA had no effect on PHT levels, but PHT significantly decreased VPA concentrations. PHT enhanced both gamma-glutamyltranspeptidase activity (gamma-GT) and D-glucaric acid excretion (GLA); these effects were potentiated by VPA. VPA alone did not affect gamma-GT, but significantly enhanced GLA.

3. Frey OR, Comparison of phenytoin serum concentrations in premature neonates following intravenous and oral administration. Ann Pharmacother. 1998 Mar;32(3):300-3

A prospective, uncontrolled study was conducted over 6 years in a university-affiliated district hospital. 2 different preparations were used for intravenous infusion and for oral therapy. Twenty premature neonates were administered intravenous and/or oral phenytoin between February 1991 and February 1997.
Nine patients received intravenous (group A) and 15 patients received oral (group B) therapy. There were no significant differences between the groups in mean +/- SD gestational age (26.1 +/- 1.37 vs. 26.9 +/- 3.30 wk), 5-minute Apgar score (8.7 +/- 1.11 vs. 7.7 +/- 2.26), daily dosage (8.1 +/- 3.86 vs. 8.1 +/- 4.21 mg/kg/d), and phenytoin serum concentration (8.7 +/- 7.36 vs. 9.6 +/- 5.83 micrograms/mL).
The authors concluded: “Contrary to data in the current literature, reliable serum concentrations in premature neonates were achieved by oral administration of phenytoin suspension. Oral therapy offers a number of advantages and considerably reduces the cost of therapy. Due to substantial variations in phenytoin pharmacokinetics in neonates, close monitoring of serum concentrations is required. Further investigation is required to confirm these results, especially in neonates younger than 20 days' postnatal age and those receiving products other than the brand leader.”

4. Gustavson LE., A single-dose study to define tiagabine pharmacokinetics in pediatric patients with complex partial seizures. Neurology. 1997 Apr;48(4):1032-7

This was an open-label study of 25 children with complex partial seizures that assessed the pharmacokinetics and safety of a single dose of approximately 0.1 mg/kg tiagabine. Seventeen children were receiving an inducing AED (carbamazepine or phenytoin); eight were receiving valproate. Tiagabine was well tolerated. Results were consistent with observations in adults taking tiagabine with inducing AEDs or valproate. Exploratory regressions on these data in children and previous data in adults showed fairly strong relationships between body size and tiagabine clearance and volume of distribution, with body size explaining about 40 to 50% of the variability. When adjusted per kg body weight, clearance and

volume were greater in children than adults. When adjusted per m2 body surface area, clearance and volume were more similar in adults and children.

5. Malik S.I. et al, Phenytoin and Phenobarbital Stable Isotope Studies in Neonates, Pediatric Neurology Vol. 29 No. 5, 2003

A pharmacokinetic study of phenytoin and phenobarbital with nonradioactive isotopes was performed in nine neonates in an intensive care unit setting. A single-pulse dose of either labeled phenobarbital (1,3-15N, 2-13C) or labeled phenytoin (2-13C, 1, 3-15N) was administered to neonates with gestational age between 25 and 40 weeks and were receiving maintenance medication. Blood samples were collected at fixed intervals, and with a computerized gas chromatography mass spectrometry system, plasma concentrations of the labeled and unlabeled drug in relation to time administered were obtained. Several kinetic characteristics related to drug absorption, clearance, and elimination were determined. The authors concluded that the use of a nonradioactive labeled isotope overcomes the limitations of conventional pharmacokinetic methodology and can be specifically useful in neonates and infants in whom volumes of distribution are rapidly changing and steady state is not achieved.

6. Ogutu BR. et al, Phenytoin pharmacokinetics and clinical effects in African children following fosphenytoin and chloramphenicol coadministration, Br J Clin Pharmacol. 2002 December; 54(6): 635–642.

Some children with malaria and convulsions also have concurrent bacterial meningitis. Chloramphenicol is used to treat the latter whereas phenytoin is used for convulsions. Since chloramphenicol inhibits the metabolism of phenytoin in vivo, we studied the effects of chloramphenicol on phenytoin pharmacokinetics in children with malaria.
Multiple intravenous (i.v.) doses of chloramphenicol succinate (CAP) (25 mg kg-1 6 hourly for 72 h) and a single intramuscular (i.m.) seizure prophylactic dose of fosphenytoin (18 mg kg-1 phenytoin sodium equivalents) were concomitantly administered to 15 African children with malaria. Control children (n = 13) with malaria received a similar dose of fosphenytoin and multiple i.v. doses (25 mg kg-1 8 hourly for 72 h) of cefotaxime (CEF). Blood pressure, heart rate, respiratory rate, oxygen saturation, level of consciousness and convulsion episodes were monitored. Cerebrospinal fluid (CSF) and plasma phenytoin concentrations were determined.
The authors concluded that a single i.m. dose of fosphenytoin provides anticonvulsant prophylaxis in the majority of the children over 72 h. However, a larger study is needed to investigate the effect of concomitant administration of multiple doses of the two drugs in this population of patients.

7. Painter MJ. et al, Neonatal phenobarbital and phenytoin binding profiles. J Clin Pharmacol. 1994 Apr;34(4):312-7

Phenobarbital and phenytoin binding profiles were determined in 27 neonates. Binding of both drugs decreased compared with that in older subjects. In vitro binding of both agents correlated significantly with total protein and albumin concentrations. In vivo binding at 0.5 hours correlated significantly with birthweight and gestational age. Phenobarbital, but not phenytoin, binding decreased when three other therapeutic agents were concomitantly administered. Bilirubin concentrations, free fatty-acid concentrations, and pH values encountered in this population did not significantly influence binding. An in vitro binding profile accurately predicted in vivo free fractions (percent drug unbound) and plasma concentrations of both drugs.

8. Sallas WM. et al, Pharmacokinetic drug interactions in children taking oxcarbazepine, Clin Pharmacol Ther 2003;74:138-49

In this trial pediatric patients (3-17 years of age) receiving an oxcarbazepine dose titrated to 30 to 46 mg/kg/d given twice daily had 1 to 4 blood samples collected per patient for population pharmacokinetic

analysis of oxcarbazepine's major bioactive 10-monohydroxy metabolite. 7 concomitant antiepileptic drugs and 12 additional covariates were examined for their effects on the pharmacokinetics of 10-monohydroxy metabolite.
Carbamazepine, phenobarbital, or phenytoin administered with oxcarbazepine increased the apparent clearance of 10-monohydroxy metabolite by 31% to 35%, whereas carbamazepine levels decreased by 15% and phenobarbital levels increased by 14%. Metabolism by CYP2C19 is the "minor" pathway of phenytoin metabolism but is known to cause clinically significant drug interactions at clinically relevant concentrations of phenytoin. In the current clinical study no such effect (increase in phenytoin levels) was seen, and compared with other known potent inhibitors of CYP2C19, the 10-monohydroxy metabolite could be considered to be a weak inhibitor of this isozyme.

9. Schwabe MJ., Wheless JW, Clinical experience with topiramate dosing and serum levels in children 12 years or under with epilepsy. J Child Neurol. 2001 Nov;16(11):806-8

The investigators reviewed topiramate dosing and corresponding serum levels (microg/mL) (n = 77) in 41 children who were treated to clinical response or tolerability. The patients were divided into older (6-12 years [n = 21]) and younger (< or = 5 years [n = 20]) groups. Topiramate was given as monotherapy (n = 9), with an enzyme-inducing antiepileptic drug (n = 16) (phenobarbital, phenytoin, or carbamazepine), or as polytherapy (n =17) (another antiepileptic drug). In the older children, there was a good dosage to serum level correspondence. However, younger children on topiramate monotherapy or co-therapy with an enzyme-inducing antiepileptic drug had relatively lower serum levels, but the serum level was increased if they were on polytherapy without an enzyme-inducing drug. This study supports a wider dosing range (7-22 mg/kg/day) of topiramate and dosage escalation beyond the approved range. Serum levels are useful in guiding topiramate dosing, especially in young children.

10. Stowe CD. et al, Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. J Clin Pharmacol. 2000 Dec;40(12 Pt 2):1452-61

The purpose of this study was to determine if phenytoin protein binding and metabolism were altered in prepubescent pediatric patients within the first 10 days following severe, acute traumatic brain injury. Patients (n = 10) received phenytoin loading doses (15-20 mg/kg) followed by a maintenance regimen (7 mg/kg/day) initiated within 12 hours of the loading dose. Phenytoin serum concentrations were measured serially on days 1, 2, 3, 5, 7, 9, and 10 at 1, 6, and 12 hours. Time-invariant and time-variant Michaelis-Menten pharmacokinetic models were fit to the unbound phenytoin concentration-time data. Albumin concentrations significantly decreased over time ($p < 0.001$) and were predictive of the phenytoin binding ratio. Rapid inhibition of metabolism was observed initially following injury. This was followed by induction of metabolism as reflected by a Vmax induced of 20.79 +/- 13.71 mg/kg/day, which was approximately twofold higher than reported values for non-stressed children. Children with severe, acute neurotrauma were found to have markedly altered protein binding and phenytoin metabolism.

11. Weintraub D. et al, Effect of Antiepileptic Drug Comedication on Lamotrigine Clearance, Arch Neurol. 2005;62:1432-1436

570 medical charts of outpatients 12 years and older seen at the Columbia Comprehensive Epilepsy Center who received lamotrigine as monotherapy or adjunctive therapy were reviewed.
Comedication with phenytoin, carbamazepine, and valproate sodium were the major AED predictors of lamotrigine serum concentration. Comedication regimens with felbamate, oxcarbazepine, and phenobarbital were small but significant predictors. Patients had significantly higher lamotrigine clearance (CL) when taking phenytoin, carbamazepine, and phenobarbital than when not taking those comedications and had significantly lower lamotrigine CL when taking valproate. No other AEDs affected lamotrigine CL. Phenytoin increases lamotrigine CL by approximately 125%, carbamazepine increases lamotrigine CL by approximately 30% to 50%, and valproate decreases lamotrigine CL by approximately 60%.
No newer AED, with the possible exception of oxcarbazepine, has a major impact on lamotrigine CL.

12. Wilson JT. et al, Loading and conventional dose therapy with phenytoin in children: kinetic profile of parent drug and main metabolite in plasma. Clin Pharmacol Ther. 1976 Jul;20(1):48-58

Epileptic children were given phenytoin (DPH) in loading (four doses of 4.4 to 6.3 mg/kg/dose given 8-hourly and then 6 mg/kg/day) or conventional (5 to 9 mg/kg/day) doses. Plasma levels of DPH and its main metabolite (p-OH-DPH) were measured by a mass fragmentographic technique. Plasma DPH levels of more than 10 mug/ml were achieved within 16 to 38 hr in the children given loading doses and within 5 days in the conventionally dosed children. No immediate side effects were noted, but within 8 to 10 days 9 of 13 children developed a generalized skin rash. Plasma p-OH-DPH (free or conjugated) paralleled DPH during the accumulation phase but not during DPH elimination. The ratio of metabolite to DPH in plasma showed both an interindividual variation and an inverse relation to the level of DPH. Identical twins in the study had a similar ratio and plasma level-time course profile. The authors concluded that the loading dose regimen achieves an appropriate plasma level of DPH rapidly, that saturation kinetics are operative for p-OH-DPH formation, that the ratio of metabolite to DPH in plasma is an individual characteristic in children, and that further studies on the delayed toxicity are needed before the loading dose regimen can be recommended.

13. Yuen GJ. et al, Phenytoin dosage predictions in paediatric patients, Clin Pharmacokinet. 1989 Apr;16(4):254-60

This study examined 2 pharmacokinetic methods to adjust phenytoin dosage based on a single dosing-rate/steady-state serum phenytoin concentration pair. A Bayesian forecaster and a fixed parameter [rate of metabolism (Vmax)] method were examined with previously published sets of a priori parameter estimates. The fixed Vmax method was utilised with the parameter derived from native Japanese (method 1), US Caucasian (method 2) and European (method 3) patients. The Bayesian forecaster used a priori parameter estimates obtained from native Japanese (method 4) and European (method 5) patients. Each method was examined retrospectively in 34 paediatric patients with a total of 48 predictions possible. There was no significant difference among the 5 methods. However, the Bayesian algorithm tended to be more robust over a broad range of situations, providing predictions in all cases. The fixed Vmax methods could not provide predictions in every case. Finally, all methods had a significant number of overpredictions of dosage. Poorer results were observed when prediction of steady-state serum concentrations was performed, partly due to the retrospective nature of the study. The authors concluded that close monitoring of patients, regardless of the method chosen to adjust dosage, is recommended.

MAH3:

1. Loughnan PM et al, Pharmacokinetic observations of phenytoin disposition in the newborn and young infant, Archives of Disease in Childhood, 1977,52,302-309

The PK profile of phenytoin was studied in 30 infants aged 2 days to 96 weeks following an intravenous (IV) loading dose of 12 mg/kg phenytoin sodium, infused over 15 to 20 minutes followed by a 8-mg/kg/day maintenance oral dose started on Day 2. The plasma phenytoin half-life (t½) during the first week of life in term infants was prolonged and very variable (20.7±11.6 hours, mean ± standard deviation [SD]). Thereafter, the plasma t½ was much shorter (7.6 ± 3.5 hours). In preterm infants, the t½ was much longer (75.4 ± 64.5 hours) and more variable. The mean apparent volume of distribution was similar in these groups of infants: preterm newborn 0.80 ± 0.22 L/kg, term infants during the first week of life 0.80 ± 0.26 L/kg, and term infants >2 weeks of age 0.73 ± 0.18 L/kg. Very low 'trough' plasma phenytoin concentrations were observed after the fourteenth postnatal day in 19 infants receiving 8 mg/kg per 24 hours orally. On the other hand, infants younger than 1 week of age receiving the same dose, especially if preterm, frequently showed drug accumulation and higher plasma phenytoin concentrations. Phenytoin plasma protein binding appeared to be lower in the newborns but approached that of adult values by the

age of 3 months. A phenytoin IV loading dose of 8 mg/kg can be expected to generate a mean plasma phenytoin concentration of 10 μg/mL in the newborns. Loading doses of up to 12 mg/kg were given without untoward effects. The authors concluded that during the first week or so of life, plasma phenytoin t½ is so variable that no fixed dosage regimen can be derived from the available data. However, beyond the second week of life a dose of 8 mg/kg per 24 hours is probably inadequate for most infants.

2. Painter MJ et al, Phenobarbital and diphenylhydantoin levels in neonates with seizures, The Journal of Pediatrics, Feb 1978

The plasma levels of phenytoin following initial administration and during maintenance therapy in 59 neonates with seizures were determined. Following phenytoin IV administration of 15 to 20 mg/kg, levels of 14.5 ± 3 μg/mL were achieved for phenytoin. Therapeutic plasma levels of phenytoin could not be achieved by oral administration (given in any form) in the neonates.

3. Forsythe W.I. et al, Phenytoin Serum Levels in Children with Epilepsy: a Micro Immuno-assay Technique, Develop. Med. Child Neurol. 1979,21,448-454

Phenytoin levels in 50 children with seizures using a micro immunoassay technique were studied. It was found that: (1) a single dose of phenytoin suspension or capsules (5 mg/kg/day) produced inadequate serum levels at 16 and 24 hours after ingestion, and for this reason, single dosage was not recommended; (2) twice daily dosage (BID) of phenytoin suspension or capsules (5 mg/kg/day) produced adequate serum levels in most children throughout the 24-hour period, and this dosage was recommended; (3) 12 children continued to have seizures but when the dose was increased to 10 mg/kg/day, 6 of the 12 obtained seizure control; (4) phenytoin reached equilibrium in the serum in 5 days provided the child had not previously been taking phenobarbitone; (5) of the 13 children who had been taking phenobarbitone, 10 did not achieve equilibrium (steady-state) of phenytoin in serum for 1 to 4 weeks; (6) phenytoin suspension given BID produced satisfactory serum levels provided the bottle was shaken well before dispensing; (7) apart from minor variations, phenytoin maintained its level in serum during the 14- to 30-month follow-up period, whether 5 mg or 10 mg/kg/day of phenytoin was given.

4. Dodson W.E., Phenytoin elimination in childhood: Effect of concentration-dependent kinetics, Neurology 30: 196-199, February 1980

The effect of phenytoin concentration on the elimination rate of phenytoin was evaluated in infants, children, and young adults ranging in age from 1 day to 22 years. As phenytoin concentration increased, the effective t½ increased. In 8 children, aged 7 months to 4.83 years with initial concentrations between 10 to 20 μg/mL, the average t½ (18.6 hours) was approximately 58% as long as the average in adults with comparable concentrations. Whereas the t½ correlated with the initial phenytoin concentrations, there was no correlation overall between t½ and age, size, or number of other antiepileptic medications taken.

5. Painter MJ. et al, Phenobarbital and phenytoin in neonatal seizures: metabolism and tissue distribution, Neurology. 1981 Sep;31(9):1107-12

Loading doses of 15 to 20 mg per kilogram of both phenobarbital and phenytoin, administered intravenously, are necessary in the newborn to achieve rapid therapeutic plasma anticonvulsant levels. Maintenance doses of 3 to 4 mg per kilogram of both agents will maintain therapeutic levels. Phenytoin is, however, not predictably absorbed by the oral route. Brain:plasma ratios were 0.71 +/- 0.21 for phenobarbital and 1.28 +/- 0.32 for phenytoin, which are in general agreement with reported adult values. The brain:plasma ratio of phenobarbital increased with gestational age. Phenytoin was found in higher concentration in gray matter, whereas phenobarbital was equally distributed between gray and white matter.

6. Blain P.G. et al, Pharmacokinetics of Phenytoin in Children, Br. J. din. Pharmac. (1981), 12, 659-661

Blain et al estimated the apparent maximal rate of phenytoin metabolism (Vmax) and Michaelis-Menten constant (Km) for phenytoin in 40 children (aged 8 to 33 months) and in 21 adults (aged 18 to 66 years). The apparent Km was similar in children (7.5 ± 1.2 mg/L) and adults (9.4 ± 2.3 mg/L). Vmax differed significantly (P <0.001) between children (20.4 ± 2.1 mg/kg/day) and adults (8.7 ± 0.7 mg/kg/day). After correction for differences in the ratio of liver weight to body weight in children and adults, Vmax was similar in both groups.

7. Dodson W.E., Nonlinear kinetics of phenytoin in children, Neurology (Ny) 1982;32:42-8

The nonlinear kinetics of phenytoin in 54 children were evaluated by measuring phenytoin concentrations at steady state at 3 or more doses. There was good correlation between phenytoin doses and concentrations when a nonlinear kinetic model was used. Increasing age was associated with a reduction in the apparent Vmax.

8. Grasela T.H. et al., Steady-state Pharmacokinetics of Phenytoin from Routinely Collected Patient Data, Clinical Pharmacokinetics 8: 355·364 (1983)

The investigators analysed previously reported routine phenytoin clinical PK data from Japan, England, and Germany to estimate population PK parameters using a nonlinear mixed effects model (NONMEM). There were 780 steady-state phenytoin concentrations and associated dosage rates (mg/day) from 322 patients including paediatric and adult patients, with mean age being 18.4±17.3 (SD) years and 53% of the patients were male. Estimates of the influence of age, sex, data source, height, and weight on Vmax and Km were obtained. The Vmax and Km of a 70 kg adult European male were estimated to be 415 mg/day and 5.7 mg/L, respectively. Vmax was not influenced by sex, age, or data source. The parameters of a power function of height and weight were estimated to adjust Vmax for body size. The best function adjusts Vmax in proportion to weight to the 0.6 power; height contained no useful information. Km was not influenced by sex. The Km for patients younger than 15 years old was 43% less than that of older patients.

9. Bauer L.A., Blouin R.A., Phenytoin Michaelis-Menten Pharmacokinetics in Caucasian Paediatric Patients, Clinical Pharmacokinetics 8: 545-549 (1983)

PK parameters were calculated in 135 epileptic paediatric patients receiving phenytoin as their only anticonvulsant therapy. Mean Vmax and Km values, respectively, were 13.95 mg/kg/day and 6.59 µg/mL for 0.5- to 3-year-old patients, 10.93 mg/kg/day and 6.82 µg/mL for 4- to 6-year-old patients, 10.05 mg/kg/day and 6.51 µg/mL for 7- to 9-year-old patients, and 8.25 mg/kg/day and 5.69 µg/mL for 10- to 16-year-old patients. Linear regression analysis of Vmax versus age revealed a significant decline in Vmax with age. However, a plot of Km versus age showed a poor correlation (r = -0.170) and a large amount of variability.
The authors concluded that the youngest age group would require on average 62% more phenytoin/kg/day than the oldest age group to maintain a steady-state phenytoin concentration of 15 µg/mL. Because of these age-related PK differences, phenytoin dosages may require adjustment as paediatric patients become older.

10. Albani M., Wernicke I., Oral Phenytoin in Infancy: Dose Requirement, Absorption, and Elimination, Pediatric Pharmacology 3:229-236 (1983)

Oral phenytoin therapy in infants required about 18 mg/kg to achieve and to maintain serum concentrations between 8 and 25µg/mL. Plasma half-life determined in 12 infants aged 6 weeks to 12 months ranged between 7.9 to 24.9 hours. Measurement of phenytoin metabolite excretion in urine during

steady state revealed that only about 30% of the daily given phenytoin is eliminated through the kidneys. Studying the bioavailability of phenytoin in different age groups before and after ingestion of age-appropriate foods showed an age-dependent absorption rate and extent and an influence of the food upon the absorption pattern could be demonstrated.

11. Kohda Y. et al, Prediction of Phenytoin Dosage for Pediatric Patients in Relation to the Plasma Phenytoin Concentration, l03rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April J983

This study examined the relationship between dose and steady-state concentration of phenytoin using selected 171 therapeutic drug level monitoring data from paediatric patients administered phenytoin. The data were analyzed by using the Michaelis-Menten equation. The maximum rate of administration, Dmax (mg/kg/day), decreased with an increase in age. In contrast, the Km, expressed as plasma phenytoin concentration at which the rate of administration is one-half the maximum rate (μg/mL), increased with an increase in age. The values of Michaelis-Menten parameters were corrected by the recalculation by using the absorbed amount of phenytoin. The corrected values of Dmax and Km were asymptotically approached the values in an adult population, respectively. The prediction of the age-related dose of phenytoin was carried out by using the Michaelis-Menten parameters, when the percentage of absorption was 100%.

12. Leff R.D. et al, Phenytoin Metabolism in Infants following Intravenous and Oral Administration, Dev. Pharmacal. Thu. 9: 217- 223 (l986)

This study examined the disposition of phenytoin in 7 infants with a mean age of 22 days and a mean weight of 3,756 g. Multiple doses of phenytoin were administered IV and/or orally as a part of required medical care. Gas chromatography/mass spectrometry was used for analyses of phenytoin and 3 metabolites, which were HPPH; methylated 3,4-catechol, and 3,4-dihydrodiol, in blood, urine, and faeces. Data from identical studies previously conducted in adults were utilised for comparison with the infants. The mean phenytoin dose (±SD) in infants was 8.1± 4.4 mg/kg/day, and the mean serum concentration (±SD) was 4.8±4.6 μg/mL. In adults, the mean dose was 5.3±0.6 mg/kg/day, and the mean serum concentration was 12.0±1.9 μg/mL. No significant differences were found between infants and adults in the pattern of urinary metabolites or in the total recovery of phenytoin and metabolites in 24-hour urine samples. The authors considered that these results indicate that metabolic pathways for phenytoin are the same in infants and adults. Absorption of an oral dose of phenytoin in infants appeared to be completely based on recoveries of drug and metabolites in urine and on the fact that less than 3% of an oral dose could be found in stools. The authors concluded that the results of these studies indicate that the low blood concentrations of phenytoin resulting from the relatively high daily dosage of phenytoin in infants, when compared to adults, cannot be explained on the basis of poor oral absorption of phenytoin; these age-related differences must be due to a relatively high metabolic clearance of the drug in infants.

13. Singh I.M. et al, Monitoring of drug therapy in epileptic children, International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol.25 No.5-1987, 251-254

Plasma phenytoin steady state levels were monitored in 20 children who were receiving phenytoin, either alone or in combination with phenobarbitone. A wide interindividual variation was observed in steady-state plasma levels. Among children who were receiving only phenytoin, nearly 50% had drug levels above 10μg/mL. It was observed that children with drug levels above 10 μg/mL exhibited good therapeutic response. Two children who presented with acute toxicity showed drug levels above 40μg/mL.

14. Suzuki Y. et al, Phenytoin Age-Dose-Concentration Relationship in Children, Therapeutic Drug Monitoring 16:145-150, 1994

Suzuki evaluated a list (N = 423) of phenytoin steady-state concentrations from children taking phenytoin alone or in combination with other drugs (N = 308) from their therapeutic drug monitoring database (from 1984 to 1990). Only 43% of concentrations were within the commonly accepted 'therapeutic' or 'reference' range (10 to 20μg/mL). Age-dose-concentration relationships showed that although occasional concentrations were above 20 μg/mL, many patients receiving commonly recommended paediatric phenytoin doses (4 to 8 mg/kg/day) achieved concentrations below the reference range, especially children younger than 3 years of age. Vmax and Km were evaluated for patients with at least 2 steady-state concentrations measured for 2 or more different daily doses. Vmax appeared to decrease significantly with age but there was no age relationship for Km.

15. O'Mara N.B. et al, Pharmacokinetics of phenytoin in children with acute neurotrauma, Critical Care Medicine, Vol23, No.8, 1995

The PK of phenytoin administered IV in 16 critically ill infants and children with various types of acute neurologic injuries (mean age, 7.6 years; range, 0.5 to 16 years) was determined. Blood samples were collected to measure total and free phenytoin concentrations in plasma. A 24-hour urine collection was made to determine the concentrations of the major metabolite of phenytoin. In 12 children who survived the acute illness, a lower-than-predicted Km and higher-than- predicted Vmax were observed. Initial free phenytoin fractions ranged between 8% and 15%. During additional free fractions measurement, some patients demonstrated an increase (9.1% to 34% increase) in free fraction but some patients demonstrated a decrease (1.8% and 19.8% decrease) in free fraction. The ratio of amount of phenytoin to phenytoin plus HPPH excreted in the urine in a 24-hour urine collection demonstrated a wide inter-patient variability.

16. Abduljabbar M. et al, Phenytoin dosage adjustment in Saudi epileptics: utilization of steady-state pharmacokinetic parameters, European Journal of Neurology 1999. 6:331-334

The investigators determined the Vmax and Km in 271 Saudi epileptic patients having generalised tonic-clonic seizures and who were treated with phenytoin. The patients comprised of 150 (55.4%) males and 121 (44.6%) females, with a mean age of 31.7 years (SD = 18.5). The mean Vmax for subjects younger than 16 years of age was 10.35 mg/kg/day (SD = 0.73, range = 3.77-17.01), whereas for those older than 16 years, the mean value was 7.99 mg/kg/day (SD = 0.15, range = 3.68-15.95). The difference was statistically significant ($P < 0.001$). Vmax was positively correlated with weight ($r = 0.953$), but negative with age ($r = -0.903$). Km values ranged from 1.01 to 20.87 mg/L. The adult Km mean of 6.52 mg/L (SD = 0.24) was significantly higher than the mean of 4.79 mg/L (SD = 0.40) for paediatric patients ($P < 0.01$), but Km was correlated neither with age nor with weight. Their results showed no difference between the predicted and observed serum phenytoin concentrations in both the paediatric and adult patients when the respective age group Km and Vmax values were used to adjust phenytoin doses. However, the paediatric cases required 30% more phenytoin per kilogram of body weight than the adults for the achievement of similar serum concentrations.

17. Kodama H. et al, In vivo binding characteristics of phenytoin to serum proteins in monotherapy pediatric patients with epilepsy, International Journal of Clinical Pharmacology and Therapeutics, Vol. 38 - No. 1/2000 (25-29)

In this study the binding characteristics of phenytoin to serum proteins in the paediatric population. Serum samples in the study were obtained from 40 paediatric patients (16 male, 24 female) receiving phenytoin monotherapy were determined. Their age ranged from 1 to 15 years. The in vivo population binding parameters of phenytoin to serum proteins and theoretical minimal unbound serum phenytoin fraction (fu) were determined using an equation derived from the Scatchard equation. The fu (0.087) in these paediatric patients is similar to the unbound serum phenytoin fraction in adult patients receiving phenytoin therapy reported by Richens (ie, 0.1). The authors concluded that the unbound serum fraction of phenytoin in paediatric patients with epilepsy can be assumed to be relatively constant in the therapeutic concentration range of phenytoin.

18. Ogutu B.R. et al, Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus, Br J Clin Pharmmcol5, 6, 1 12- 119, 2003

Ogutu et al studied the PK and clinical effects of phenytoin and fosphenytoin sodium in children with severe falciparum malaria and status epilepticus. Children received phenytoin IV as a 18-mg/kg loading dose infused over 20 minutes followed by a 2.5-mg/kg 12-hourly maintenance dose infused over 5 minutes (N=11). After administration, a plasma unbound phenytoin concentration of more than 1 μg/mL was attained within 5 to 20 minutes. Mean (95% confidence interval, CI) steady state free phenytoin concentrations were 2.1 μg/mL (1.7, 2.4; n = 6). Median times (range) to peak plasma phenytoin concentrations following the loading dose were 0.37 (0.33-0.67) hours. These PK data suggest that unbound phenytoin concentrations within the therapeutic range (1 to 2 μg/mL) were achieved within 5 to 20 minutes after IV administration of phenytoin at the above-mentioned dosing regimen. Mean steady state unbound concentrations were maintained within the therapeutic range for 48 hours.

19. Al Za'abi M. et al, Application of Routine Monitoring Data for Determination of the Population Pharmacokinetics and Enteral Bioavailability of Phenytoin in Neonates and Infants With Seizures, Ther Drug Monit 2006;28:793–799

Al Za'abi investigated the population PK and the enteral (oral and nasogastric) bioavailability of phenytoin in neonates and infants with seizures. Data from 83 patients were obtained retrospectively from medical records. A 1-compartment model was fitted to the log-transformed concentration data using NONMEM. Between-subject variability and interoccasion variability were modeled exponentially together with a log transform, bothsides exponential residual unexplained variance model. Covariates in nested models were screened for significance. Model robustness was assessed by bootstrapping with replacement (N = 500) from the study data. The parameters of the final PK model were clearance (L/h) = 0.826.[weight (WT, kg) / 70]0.75.[1 + 0.0692.(postnatal age (days) - 11)]; volume of distribution (L) = 74.2.[WT (kg) / 70]; absolute enteral bioavailability = 0.76; absorption rate constant (h) = 0.167. The between-subject variability for clearance and volume of distribution was 74.2% and 65.6%, respectively. The interoccasion variability for clearance was 54.4%. The unexplained variability was 51.1%. Final model parameter values deviated from median bootstrap estimates by less than 9%.
The authors concluded: "Phenytoin disposition in neonates and infants can be described satisfactorily by linear PK. The values of allometrically scaled clearance and volume were similar to adult values, suggesting no major kinetic differences between adults and infants on the basis of size alone. Postnatal age independently influenced clearance. Switching from enteral to IV routes may require a dosage adjustment. The results of this study provide a basis for more rational prescribing of phenytoin in infants and neonates."

20. Cheng A, Banwell B, Levin S, Seabrook JA, Freeman D, Rieder M, Oral Dosing Requirements for Phenytoin in the First Three Months of Life, J Popul Ther Clin Pharmacol Vol 17(2) Summer 2010

Cheng et al investigated the phenytoin oral dose required to achieve therapeutic blood concentrations without clinical toxicity in the first weeks of life. 8 infants aged 2 weeks to 3 months with seizures were treated with phenytoin. Total and free phenytoin concentrations, and urine phenytoin metabolite (p-hydroxyphenytoin) were measured every 2 weeks. Parents were asked to note seizure frequency and complete a questionnaire about possible side effects every 2 weeks. No infants had seizures and no clinical side effects were noted. Doses required to achieve therapeutic serum concentrations ranged from 10 to 20 mg/kg/day, considerably higher than doses required in adults. Free phenytoin levels were 8% to 13% of total serum concentrations, similar to ratios reported in adults. The authors concluded that to achieve therapeutic serum phenytoin levels in infants, doses of 10 to 20 mg/kg/day are required and these higher doses can be safely administered without clinical toxicity.

21. Buchanan RA. et al, Single daily dose of diphenylhydantoin in children, The Journal of Pediatrics, Vol. 83, No. 3, pp. 479483, Sep 1973

Once daily administration of the 24-hour phenytoin anticonvulsant requirement was studied in 28 children. All patients received approximately 5 mg/kg/day of phenytoin. Fourteen patients received the capsule formulation (mean age = 8.3 years) and 14 received the chewable tablets (mean age = 5.2 years). Levels obtained 24 hours after administration of the dosage were the same as those at 12 hours, indicating no tendency for subtherapeutic levels just prior to the next dose. None of the patients demonstrated any significant change in seizure control when single daily administration was compared to divided daily administration. The authors support the single daily administration of phenytoin due to potential advantages; reduced hospital nursing costs, patient convenience, and improved seizure control due to better reliability.

Comments:

PHT can be administered orally, intravenously, rectally and intramuscularly. No data have been submitted regarding the rectal route of administration in children. The rapporteur did not identify any phenytoin products which are licensed for rectal administration. A review (Smith S, 2001) examined pharmacokinetic data for different AEDs with the aim of determining whether the rectal route of administration for these drugs is advisable in children. The authors concluded that phenytoin is poorly soluble and not well absorbed when administered rectally and therefore its use via this route is not recommended.
In addition, there is little information regarding the IM administration (see previous comments on pages 11-12).

From the submitted studies, it appears that IV administration can produce plasma concentrations within the therapeutic range in a more reliable manner than with oral dosing which results in a wide range of blood drug levels.
Oral administration in children is recommended to be twice daily (BNF for children/BNF-C and Martindale: The Complete Drug Reference). In the study by Forsythe et al (1979) single doses of oral PHT produced inadequate serum levels, whereas twice daily dosing produced satisfactory serum levels.

Albani et al (1883) demonstrated an age dependent influence of food on the absorption of PHT, by about 50% in infants, 26% in children and 13% in adolescents. They also showed that infants required much larger doses to achieve comparable serum levels to older children and suggested that this is because of incomplete oral absorption that improves over time. In addition, Painter et al found that therapeutic plasma levels of PHT could not be achieved in neonates by oral administration of doses as high as 12mg/kg/day, irrespective of formulation, due to poor GI absorption. On the other hand, Frey OR (1998) demonstrated reliable serum concentrations in premature neonates by oral administration of PHT. As discussed later in this section, other authors attribute higher dose requirements in infants to altered metabolism and not to poor absorption. However, all authors conclude that close monitoring of serum concentrations is required and further research is needed to determine PK properties in this age group.
PHT is extensively bound to plasma proteins (90%). It appears that in neonates this binding is reduced (Loughnan PM et al, 1977, Painter MJ, 1981, Painter MJ 1994). Painter stated that this can be explained in part by decreased gestational age, birth weight, total protein concentrations as well as the number of concomitantly administered medications. BNF-C states that therapeutic plasma PHT concentrations are reduced in first 3 months of life because of reduced protein binding (6-15µg/ml compared to 10-20µg/ml in children over 3 months).

PHT is primarily metabolised in the liver, mainly via CYP2C9 and to a lesser extent by CYP2C19. The main metabolite of phenytoin is p-hydroxyphenylhydantoin (HPPH). Most PHT is excreted in the urine in the form of inactive metabolites. The extent and pattern of the excretion of PHT metabolites do not show

any age related changes. At steady state, the HPPH/phenytoin plasma concentration ratio shows considerable inter-individual variability. Slow and fast PHT metabolisers have been identified in children (Battino D. et al, 1995). It is also noted that CYP2C9 activity is very low just prior to birth and increases quickly in the first year of life. In neonates, PHT elimination is low. Both phase 1 and phase 2 metabolism are slower at birth than later. This immaturity of hepatic metabolism is reflected in prolonged half-lives and decreased clearance in this age group (Koren Gideon, 1997).

Bauer LA et al (1983), Suzuki Y et al (1994) and Abduljabbar M et al (1999) found that Vmax decreases significantly with age. Leff RD et al (1986) hypothesised that these age-related differences in dose requirements must be due to a relatively high metabolic clearance of the drug in infants. However, Blain and Grasela, after correcting for differences in the liver/bodyweight ratio or bodyweight adjusted for body size respectively, found that Vmax is similar between children and adults. Battino D et al in their review regarding the clinical pharmacokinetics of AEDs in children (1995) expressed the view that the difference in dose requirements between children and adults could be due to the greater relative weight of the liver in children and not to any qualitative or quantitative differences in the activities of the enzyme involved in the metabolism of PHT.

PHT is a classic example of a drug following non-linear pharmacokinetics. As the dose of PHT increases, the clearance rate decreases (as the enzyme system becomes increasingly saturated). Half-life also changes with PHT dosages and the higher the dose, the longer the half-life. It is therefore relatively easy to exceed the normal therapeutic levels with moderate changes in the administered doses.
Monitoring is mandatory during PHT therapy, although for other AEDs therapeutic drug monitoring is recommended only in certain cases (to assess clinical toxicity, compliance, to attain an individual therapeutic concentration), (Patsalos PN et al, 2008).
Total serum PHT is commonly measured in everyday clinical practice. However, unbound serum concentrations may be more useful in certain conditions where PHT plasma protein binding is changed (liver disease, renal disease, nephrotic syndrome, hyperbilirubinemia, displacement by concomitant drug administration and other).

Many drugs are known to interact with PHT. PHT is an inducer of many CYP450 enzymes and therefore can cause decreased blood levels for other drugs metabolised in the liver.
Studies were submitted examining PHT interactions with corticosteroids, valproate, tiagabine, chloramphenicol, carbamazepine, lamotrigine. Most of these drug interactions are included in the SmPC of the brand leader. Tiagabine is not mentioned in the list of drugs interacting with PHT in the SmPC of the brand leader.
Tiagabine does not appear to affect the steady-state pharmacokinetics of PHT in adults (Gustavson LE et al, 1998). The study presented by the MAH (Gustavson LE, 1997) was a paediatric study, however, only one child was on PHT at baseline and therefore no robust conclusions on the effect of tiagabine on paediatric patients on PHT can be drawn.

From the available literature, the rapporteur has drawn the following main conclusions regarding the PK properties of PHT in children:

- PHT exhibits non-linear pharmacokinetics. A small increase in the dose can cause a large change in the level of PHT in the blood.
- There is marked inter-patient variability in PHT pharmacokinetics
- The half-life of PHT is shorter in children
- In clinical practice it is often difficult to achieve the desired plasma concentration. Most often optimal control of seizures without toxicity occurs with serum levels of total PHT between 10 and 20µg/ml. However, some patients can achieve therapeutic control or exhibit side effects with sub-therapeutic levels and conversely in some patients "toxic levels" of PHT are not associated with clinical adverse effects.
- Therapeutic drug monitoring of serum drug levels to achieve target therapeutic concentration is

paramount for use of PHT in the paediatric population

The rapporteur concludes that the data submitted from the MAHs adequately describe the various aspects of pharmacokinetics of PHT in children. No new data have been identified regarding the pharmacology of PHT, other than what is already known and mentioned in the products' SmPCs.

Therefore, no SmPC changes are warranted regarding the PK properties of PHT in children.

b. Clinical efficacy

Three MAHs submitted reports from published literature regarding the efficacy of PHT in children and clinical overviews based on these reports. MAH2 cited 52 publications but individual reports or an overview of the results of the literature search were not provided.

MAH1:

1. Strotzka H. Die Kombinationsbehandlung der behandlungsresistenten Epilepsie (Combination treatment of therapy-resistant epilepsy), Wiener Klinische Wochenschrift (Vienna Clinical Weekly) 1951, 101/24-25: 465-468

This study of 227 patients suffering from epilepsy resistant to bromide and phenobarbital was conducted over 18 months in an epilepsy clinic in Vienna. From the total 227 patients, 140 were followed for a period long enough to allow reasonable outcome assessment (at least six months) and 112 were included in the statistical analysis. Fifteen patients were aged 0-10 years and 24 patients were aged 11-20 years. A total of 20 patients were treated with PHT. Nine of these patients experienced a 50-100% improvement of their disease. The author considered the antiepileptic treatment with the – at that time novel – hydantoin preparations was clearly superior to the hitherto existing therapeutic options and hence indispensable.

2. Grinschgl G., Pakesch E. Die Kombinationsbehandlung zerebraler Krampfanfälle unter besonderer Berücksichtigung der Epilepsie (Combination treatment of cerebral seizures with special consideration of epilepsy), Wiener Klinische Wochenschrift (Vienna Clinical Weekly) 1952, 64/20: 362-365

This study presents the results of a clinical investigation in 131 patients suffering from epileptic seizures. Some of the patients had been resistant to therapy with bromide and barbiturate since many years. The patients were treated with a combination therapy consisting of boron and a hydantoin preparation . In – predominantly juvenile – patients who presented with "petit mal" seizures or mixed seizure forms, an oxazolidine preparation was accessorily added or replaced for the hydantoin drug. The authors observed a clear therapeutic superiority of the boron-hydantoin treatment over the bromide-barbiturate combination both regarding efficacy and tolerance due to avoiding of hypnotic and psychic adverse effects. Furthermore, in the authors' opinion the administered hydantoin preparations were beneficial not only in patients with mixed seizure forms including "petit mal" and "grand mal" seizures, but – in low dosages – also in cases of isolated "petit mal" seizures without "grand mal" seizures. They even suggested that due to these small hydantoin doses, lower amounts of oxazolidine preparations might be required in such patients.

3. Albani M., An effective dose schedule for phenytoin treatment of status epilepticus in infancy and childhood, Neuropadiatrie 8: 286-292 (1977)

15 infants and children aged 3 days to 12.2 years suffering from status epilepticus or recurring convulsions for various clinical reasons were treated with intravenous phenytoin. After reaching the upper therapeutic

range (defined by the author as 8-25 μg/ml) within 24 hours these serum concentrations were maintained over the next days. Twelve of fifteen – including five newborns and infants below four months of age – were thus successfully treated. In the remaining three in whom phenytoin had no effect, no other anticonvulsant drug or combination of several other drugs were successful. The author recommended that infants during the first year of age, particularly during the newborn period, should be treated with 30-35 mg/kg on the first day and 20-25 mg/kg on the second day to achieve serum levels in the upper therapeutic range. In older children the dose recommended was 25-30 mg/kg and 15-20 mg/kg respectively. With this regimen, toxic side effects, such as nausea, nystagmus or vomiting were only observed in one child on the third day of treatment with a serum concentration slightly above the therapeutic range.

MAH2:

1. A survey of 156 seizure patients in a general paediatric clinic, Abernathy R.S., 1966

This was a retrospective, uncontrolled study of 156 epilepsy patients 1-17 years of age seen over 18 weeks in a paediatric clinic. The study examined the relationship between control of seizures and mental ability, presence of organic brain damage, EEG findings. Seizures were considered controlled in 71 children. 90% of patients whose epilepsy was controlled were on phenobarbital or phenytoin or a combination of those two.

2. Bacon C.J. et al, Placebo-controlled study of phenobarbitone and phenytoin in the prophylaxis of febrile convulsions, The Lancet, Volume 318, Issue 8247, 19 September 1981, 600–604

Of 138 children who had a first febrile convulsion before their second birthday, 48 were treated with phenobarbitone, 47 with phenytoin, and 43 with a placebo for 12 months. Drug levels were monitored and adverse effects of the drugs were noted. The authors concluded: "Compared with placebo, phenobarbitone significantly reduced recurrences among children under 14 months old at the time of their first convulsion, but not among older children. Phenytoin was an ineffective prophylactic agent. Ideal drug levels were difficult to maintain, and many recurrences occurred when concentrations were suboptimal. Behavioural disturbance in children taking phenobarbitone was not a serious problem. The decision to give continuous prophylaxis for febrile convulsions is complex. For children who have a first seizure before 14 months of age prophylaxis may be advisable and phenobarbitone is effective."

3. Bartha A.I. et al, Neonatal Seizures: Multicenter Variability in Current Treatment Practices, Pediatric neurology Vol. 37 No. 2, 2007

Standardized approaches to the treatment of neonatal seizures remain undeveloped. This study assessed the type and number of anticonvulsants selected, blood levels attained, and post discharge anticonvulsant treatment of neonatal seizures among five neonatal intensive care units in the United States between 2000-2003. Almost all of the 480 neonates (94%) with seizures were treated, initially with phenobarbital (82%), lorazepam (9%), phenytoin (2%), other anticonvulsants (1%), or a combination of the first two drugs (6%). While the majority of neonates were treated with one drug (59%), the number of anticonvulsants varied, as did the peak serum phenobarbital levels. The majority (75%) of survivors received anticonvulsant treatment after discharge. These neonates were more likely to have had abnormal electroencephalography or brain imaging, or to have needed a second anticonvulsant, compared with neonates whose drug therapy was discontinued. Anticonvulsant therapy is used in the majority of neonates with seizures, mostly with phenobarbital, and treatment is continued beyond discharge. The observed wide therapeutic variability may reflect a lack of standardized diagnostic and treatment approaches, particularly for seizures refractory to initial phenobarbital therapy. Trials of anticonvulsants with long-term neurodevelopmental follow-up are needed to develop evidence-based treatment guidelines.

4. Bowe J.C. et al, Evaluation of Folic Acid Supplements in Children Taking Phenytoin. Developmental Medicine & Child Neurology, 13: 343–354, 1971

A double-blind, cross-over test of folic acid and placebo was carried out in children who had a folate deficiency due to prolonged treatment with phenytoin. Despite large and long- lasting increases in blood folate levels, no associated changes were found in the frequency of fits, EEG, behaviour or gingival conditions. The trial therefore failed to reveal a relationship between the anti-folate effects of phenytoin and its anticonvulsant action.

5. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Canadian Study Group for Childhood Epilepsy. Epilepsia. 1998 Sep;39(9):952-959

This study compared the effectiveness of monotherapy clobazam (CLB) to carbamazepine (CBZ) and phenytoin (PHT) in children with epilepsy. Children aged 2-16 years with newly diagnosed epilepsy or previous failure of one drug (for poor efficacy or side effects) were assigned to one of two study arms and then randomized: CLB versus CBZ or CLB versus PHT. Eligible children had partial epilepsies or only generalized tonic-clonic seizures. Blinding used a "double dummy" technique with blinded medication serum levels (6-point scale). Intention to treat analysis using survival curves assessed the primary endpoint: length of retention on the initial medication during the year after randomization.
Fifteen centres entered 235 patients: 159 randomized to CLB versus CBZ and 76 to CLB versus PHT. Altogether, in all study arms, 119 received CLB, 78 CBZ, and 38 PHT. Overall, 56% continued to receive the original medication for 1 year with no difference between CLB and standard therapy (CBZ and PHT). Seizure control was equivalent for all three medications, as were side effects. PHT and CBZ induced more biologic side effects, such as rash, while CLB induced slightly more behavioural effects. Tolerance developed in 7.5% of patients receiving CLB, 4.2% with CBZ and 6.7% with PHT.
The authors concluded that CLB should be considered as "first line" monotherapy along with CBZ and PHT for all partial and selected generalized childhood epilepsies.

6. Castro Conde J.R. et al, Midazolam in neonatal seizures with no response to phenobarbital, Neurology 2005;64;876-879

The outcome of 45 neonates with EEG-confirmed seizures (ESz) was analyzed with regard to treatment. ESz persisted in 17 of 32 neonates receiving phenobarbital/phenytoin (13 had a poor outcome, 4 died). In contrast, ESz were rapidly controlled in 13 of 13 nonresponders to phenobarbital/ phenytoin treated with midazolam (4 had poor outcome, 2 died). Nonresponders to phenobarbital/phenytoin had a significantly worse outcome than responders did. Midazolam effectively controlled ESz in nonresponders to phenobarbital/ phenytoin and correlated with significantly improved long-term neurodevelopment.

7. Conners C.K. et al, Treatment of Young Delinquent Boys with Diphenylhydantoin Sodium and Methyphenidate: A Controlled Comparison, Arch Gen Psychiatry. 1971;24(2):156-160

Forty-three delinquent boys were randomly assigned to double-blind treatment with diphenylhydantoin sodium, methylphenidate, or placebo for two weeks. Ratings of symptoms by cottage parents and teachers, a measure of frustration, the Porteus Mazes, and an interview were used to assess the effects of the treatments. None of the measures showed effects attributable to the drugs, and subjective reports tended to show negative effects of the active drugs. The danger of random assignment studies was demonstrated, however, by the fact that the more disturbed children were assigned by chance to the placebo group. The lack of severe symptomatology, the short period of treatment, and the heterogeneous nature of the sample were considered by the authors as possible explanations of the apparent lack of beneficial effects of the two drugs.

8. Hussain N. et al, Aetiology, course and outcome of children admitted to paediatric intensive care with convulsive status epilepticus: A retrospective 5-year review, Seizure (2007) 16, 305—312

A retrospective case note study of the aetiology and course of children in convulsive status epilepticus (CSE) admitted to a large paediatric intensive care unit (PICU) was undertaken between January 1999 and April 2004. Status epilepticus was defined as a prolonged (>30 min) tonic—clonic seizure irrespective of whether the seizure had stopped prior to admission to PICU. During this period, 137 (74 male) children aged 1 month to 15 years were admitted to PICU with 147 episodes of status epilepticus. Forty-seven of the 137 children (34%) were admitted following a prolonged febrile seizure. Thirty-eight of the 137 children (28%) had a remote symptomatic cause for the CSE, 24 (18%) were admitted for an acute symptomatic cause and 15 (11%) were admitted with an acute exacerbation of a pre-existing idiopathic/ cryptogenic epilepsy. Six children had a progressive encephalopathy and no cause was identified in the remaining 7 of the 137 children (5%). Forty-nine (36%) of the 137 children had pre-existing epilepsy. The mean duration of CSE was 44 min. Forty-nine (36%) children admitted to PICU who had received a benzodiazepine with either phenobarbital or phenytoin, required further treatment to terminate the presenting episode of CSE. Forty-two of these 49 were treated with thiopentone anaesthesia and the remaining 7 with a continuous infusion of midazolam, successfully terminating status in all. No child died. Of the 70 children considered to be previously neurologically and developmentally normal prior to admission, only 1 child demonstrated a new gross neurological abnormality at the time of latest follow-up. Seven patients (5%) developed new or de novo epilepsy.

9. Koul R., Eight-year Study of Childhood Status Epilepticus: Midazolam Infusion in Management and Outcome. Journal of Child Neurology/Volume 17, Number 12, December 2002

Sixty-eight children 2 months to 14 years of age were admitted with status epilepticus to Sultan Qaboos University Hospital from November 1993 to December 2001. Thirty-eight children (55.9%) had refractory status epilepticus and 30 (44.1%) had established status epilepticus. The children with refractory status epilepticus had received intravenous or rectal diazepam and intravenous phenytoin/phenobarbital (either or both) before continuous infusion of midazolam was given. Fifty-one children received continuous midazolam infusion. In 38 children with refractory status epilepticus, the midazolam infusion was given in addition to the long-acting antiepilepsy drug, whereas 13 (18.8%) children needed only midazolam to control the established status epilepticus. Seventeen (25%) children were controlled with phenytoin sodium alone. Midazolam was given 0.15 mg/kg/minute initially as bolus in 1 minute, followed by 1 to 7 μgram/kg/minute as continuous infusion. The status could not be controlled in one child (1.5%) suffering from neurodegenerative disease. Two children needed mechanical ventilation following prolonged apnea after diazepam administration in one and diazepam plus phenobarbital in the other. No metabolic derangements or compromise of vital functions was noted on midazolam infusion. All children made a complete recovery. There was one death related to meningoencephalitis.

10. McBride MC. et al, Electrographic seizures in neonates correlate with poor neurodevelopmental outcome. Neurology. 2000 Aug 22;55(4):506-13

The EEG and outcome data were reviewed from 68 infants who met at-risk criteria for neonatal seizures and underwent prolonged continuous EEG monitoring. Forty infants had electrographic seizures (ESz). The control group contained 28 infants monitored for at least 18 hours and found not to have ESz. Outcomes for both groups were evaluated using hospital and follow-up clinic records and a standardized telephone interview.
The etiology of ESz included asphyxia (n = 23), stroke (n = 7), and other (n = 10, intraparenchymal, subdural, and subarachnoid bleeding; meningitis; sepsis; hyponatremia; and unknown). The cumulative recorded ESz duration was 8 minutes to 30 hours. Forty-three percent of infants with ESz spent 38 minutes to 32 hours in electrographic status. Despite doses of 40 mg/kg of phenobarbital and 20 mg/kg of phenytoin, 30% of infants continued to have ESz. Ten infants with ESz and one without died from causes related to neurologic instability. The occurrence of ESz was correlated with microcephaly (p = 0.04), severe cerebral palsy (CP) (p = 0.03), and failure to thrive (p = 0. 03). In the subgroup of infants with asphyxia, those with ESz were more likely to die of neurologic causes (p = 0.02) and have microcephaly

(p = 0.05) or severe CP (p = 0.04). Additionally, those with the greatest number of ESz were more likely to have these severe outcomes.
The authors stated that these data indicate an association between the amount of electrographic seizure activity and subsequent mortality and morbidity in at-risk infants in general and in infants with perinatal asphyxia. The authors concluded that only with more effective treatment of neonatal electrographic seizures can their potential contribution to poor neurodevelopmental outcome, independent of degree of insult, be ascertained.

11. Morton LD., Clinical experience with fosphenytoin in children. J Child Neurol. 1998 Oct;13 Suppl 1:S19-22; discussion S30-2

Fosphenytoin, a phenytoin prodrug, can be administered in a variety of intravenous diluents and has a more neutral pH value than phenytoin. The pharmacokinetics, safety, and tolerability of fosphenytoin in children from 1 day to 16 years old have been evaluated in two multicenter studies. Data are available from 78 patients who received loading doses (62 with intravenous administration and 16 with intramuscular administration). In these studies, fosphenytoin was converted to phenytoin within 8.3 minutes (range, 2.5-18.5 minutes). In addition, no significant difference in conversion rates was noted from the youngest to the oldest patient. No deaths or serious, alarming, or unexpected adverse events occurred; most adverse events were consistent with those seen with phenytoin therapy in adults. Both intravenous and intramuscular administrations were well tolerated, with mild bruising, tenderness, swelling, and/or erythema seen at infusion and injection sites in a small number of patients.

12. Offringa M., Newton R., Prophylactic drug management for febrile seizures in children (Review), The Cochrane Library 2012, Issue 4

No clinically important benefits for children with febrile seizures were found for intermittent oral diazepam, phenytoin, phenobarbitone, intermittent rectal diazepam, valproate, pyridoxine, intermittent phenobarbitone or intermittent ibuprofen, or for diclofenac versus placebo followed by ibuprofen, acetominophen or placebo. Adverse effects were reported in up to 30% of children. Apparent benefit for clobazam treatment in one recent trial needs to be replicated to be judged reliable. The authors concluded that given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management and, most importantly, the benign nature of the phenomenon.

13. Painter JP. et al., Phenobarbital compared with phenytoin for the treatment of neonatal seizures, N Engl J Med 1999; 341:485-489 August 12, 1999

Seizures occur in 1 to 2 percent of neonates admitted to an intensive care unit. The treatment is usually with either phenobarbital or phenytoin, but the efficacy of the two drugs has not been compared directly.
From 1990 to 1995, we studied 59 neonates with seizures that were confirmed by electroencephalography. The neonates were randomly assigned to receive either phenobarbital or phenytoin intravenously, at doses sufficient to achieve free plasma concentrations of 25 μg per milliliter for phenobarbital and 3 μg per milliliter for phenytoin. Neonates whose seizures were not controlled by the assigned drug were then treated with both drugs. Seizure control was assessed by electroencephalographic criteria.
Seizures were controlled in 13 of the 30 neonates assigned to receive phenobarbital (43 percent) and 13 of the 29 neonates assigned to receive phenytoin (45 percent; P=1.00). When combined treatment is considered, seizure control was achieved in 17 (57 percent) of the neonates assigned to receive phenobarbital first and 18 (62 percent) of those assigned to receive phenytoin first (P=0.67). The severity of the seizures was a stronger predictor of the success of treatment than was the assigned agent.
Neonates with mild seizures or with seizures that were decreasing in severity before treatment, were more likely to have their seizures end, regardless of the treatment assignment.

14. Scher MS. et al, Uncoupling of EEG-Clinical Neonatal Seizures After Antiepileptic Drug Use, Pediatr Neurol 2003;28:277-280

A prospective study of the efficacy of seizure cessation by phenobarbital versus phenytoin administration utilized both clinical and electroencephalographic expressions of seizure behaviours. The phenomenon of uncoupling was defined as the persistence of electrographic seizures despite the suppression of >50% clinical seizures after either one or both antiepileptic drugs use. Fifty-nine neonates (25 to 43 weeks estimated gestational age) with electrically-confirmed seizures were assigned to either of two drugs and continuously monitored over a 24-hour period. Nine of the fifty-nine patients had only electrographic seizure expression both before and after drug administration. Of the remaining 50 patients who had both electrical and clinical seizure expression before treatment, 24 infants responded to the first choice of an antiepileptic drug with no further seizures. Fifteen of the remaining 26 infants (58%) with persistent seizures after treatment had uncoupling of electrical and clinical expressions of seizures; no difference in the uncoupling effect was noted for neonates who were treated with either antiepileptic drug or based on prematurity or gender. The authors consider that serial electroencephalographic monitoring helps document continued electrographic seizure expression after antiepileptic drug use, following complete or partial suppression of clinical seizure behaviours.

15. Shope JT. Intervention to improve compliance with pediatric anticonvulsant therapy, Patient Couns Health Educ. 1980 3d Quart;2(3):135-41

Daily anticonvulsant drug therapy is the major treatment of seizure disorders. Compliance with the prescribed therapy is essential but not always achieved. Among 201 paediatric seizure clinic patients taking phenobarbital and phenytoin, 70 (35%) were judged noncompliant on at least one medication. The mothers of these patients were randomly assigned to experimental or control groups. An educational intervention in the form of a mothers' group discussion led by the clinic social worker was tested. On follow-up, medication compliance in the intervention group was judged significantly greater than that of the control group.

16. Young B. et al, Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures, Childs Brain 1983;10:185–192

This was a randomized, double-blind, placebo-controlled study to determine whether phenytoin administered soon after a head injury lessens the incidence of late post-traumatic epilepsy in children. 41 patients were randomized into either a phenytoin or placebo group and followed for 18 months. The patients were administered phenytoin or placebo intravenously or intramuscularly within 24 h of hospital admission. The patients were parenterally administered phenytoin or placebo until oral doses could be tolerated. There was no significant difference in the percentage of children having seizures in the treated and placebo groups ($p = 0.25$).

17. Young KD. et al, A Randomized, Double-Blinded, Placebo- Controlled Trial of Phenytoin for the Prevention of Early Posttraumatic Seizures in Children With Moderate to Severe Blunt Head Injury, Ann Emerg Med. 2004;43:435-446

Children younger than 16 years and experiencing moderate to severe blunt head injury were randomized to receive phenytoin or placebo within 60 minutes of presentation at 3 pediatric trauma centers. The primary endpoint was posttraumatic seizures within 48 hours; secondary endpoints were survival and neurologic outcome 30 days after injury. A Bayesian decision-theoretic clinical trial design was used to determine the probability of remaining posttraumatic seizure free for each treatment group.
102 patients were enrolled, with a median age of 6.1 years. 68 percent were boys. The 2 treatment groups were well matched. During the 48-hour observation period, 3 (7%) of 46 patients given phenytoin and 3 (5%) of 56 patients given placebo experienced a posttraumatic seizure. There were no significant differences between the treatment groups in survival or neurologic outcome after 30 days. According to

these results, the probability that phenytoin has the originally hypothesized effect of reducing the rate of early posttraumatic seizures by 12.5% is 0.0053. The probability that phenytoin has any prophylactic efficacy is 0.383. The median effect size in this trial was –0.015 (seizure rate increased by 1.5% in the phenytoin group), 95% probability interval –0.127 to 0.091 (12.7% higher rate of posttraumatic seizures to a 9.1% lower rate of posttraumatic seizures with phenytoin).
The authors stated that the rate of early posttraumatic seizures in children may be much lower than previously reported. Phenytoin did not substantially reduce that rate.

MAH3:

1. ***Brevoord J. C.D. et al, Status Epilepticus: Clinical Analysis of a Treatment Protocol Based on Midazolam and Phenytoin, J Child Neurol 2005;20:476-481***

This study demonstrated the clinical efficacy of phenytoin when combined with midazolam in treating generalized convulsive status epilepticus in children (N = 122). Patients' ages ranged from 0.5 to 197.4 months. Patients were treated with the following regimen (each subsequent step was taken if clinical evidence of seizures persisted): midazolam 0.5 mg/kg rectally or 0.1 mg/kg IV. After 10 minutes: midazolam 0.1 mg/kg IV. After 10 minutes: phenytoin 20 mg/kg IV in 20 minutes. After phenytoin load: midazolam 0.2 mg/kg IV followed by midazolam 0.1 mg/kg/hour continuously, increased by 0.1 mg/kg/hour every 10 minutes to maximum 1 mg/kg/hour. Phenobarbital 20 mg/kg IV or pentobarbital 2 to 5 mg/kg IV load, 1 to 2 mg/kg/hour continuous IV. Most (89%) patients were managed on midazolam and phenytoin. Midazolam and phenytoin combination given for children with generalised convulsive status epilepticus was clinically effective in 89% of patients.

2. Sicca F. et al, Phenytoin administration in the newborn and infant, Brain & Development 22 (2000) 35-40

This study evaluated the efficacy and safety of phenytoin in the treatment of situation-related seizures and epilepsies in the newborn and infant; the clinical histories of 82 patients were retrospectively reviewed. Age at seizure onset ranged from birth to 24 months (mean = 3.8 months). Sixty patients received phenytoin IV for status epilepticus, followed by long-term oral administration for 27 of them. The other 22 patients had oral treatment only. Age at the beginning of phenytoin treatment ranged from 1 day to 24 months (mean = 7.4 months). Intravenous administration made 55% of these patients seizure-free, whereas oral administration produced lasting seizure control in only 9.1%. The authors concluded: "In the first 2 years of life, IV administration of phenytoin is useful for neonatal situation-related seizures or status epilepticus, and for status epilepticus complicating chronic epilepsy. However, chronic oral treatment should not be advised because of inefficacy, difficulty to achieve therapeutic plasma levels and frequent occurrence of side effects."

3. Lewis RJ et al, 1993, Clinical Predictors of Post-Traumatic Seizures in Children With Head Trauma

In this retrospective study, clinical characteristics associated with early post-traumatic seizures in children (aged 3 months to 15 years) with head trauma were determined. Of 194 patients, 96% suffered blunt trauma and 53% had a loss of consciousness. Eighteen patients (9.3%) suffered post-traumatic seizures. A loss of consciousness, a low Glasgow Coma Scale (GCS) score (3 to 8), and an abnormal computerized tomography scan were associated with post-traumatic seizures ($P < 0.02$, 0.001, and 0.02, respectively). However, only a low GCS score was predictive of post-traumatic seizures when these factors were considered simultaneously ($P < 0.001$), with 38.7% of patients with low GCS scores suffering post-traumatic seizures and 3.8% of patients with high GCS scores suffering post-traumatic seizures. In children with low GCS scores, treatment with phenytoin was associated with a decrease in post-traumatic seizures. The authors concluded that prophylactic phenytoin reduces post-traumatic seizures in the paediatric head trauma patient with a low GCS score.

4. Callaghan N. et al, 1985, A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. Journal of Neurology, Neurosurgery, and Psychiatry 1985;48:639–44

This study demonstrated efficacy of phenytoin compared to carbamazepine and sodium valproate as monotherapy in previously untreated and recently diagnosed patients (N=181; age range, 4 to 72 years) with epilepsy. Excellent response was shown in 73% of patients with generalised seizures who received phenytoin, 39% of patients who received carbamazepine and 59% of patients on valproate. Overall response was excellent (57.1%) in phenytoin-treated patients with partial seizures with or without secondary generalised attacks, compared with 44.4% in valproate-treated patients and 33.5% in carbamazepine-treated patients. The authors concluded that sodium valproate, carbamazepine, and phenytoin were effective in the control of generalised and partial seizures and that all 3 drugs can be prescribed as an anticonvulsant of first choice.

5. Borofsky LG. et al, Diphenylhydantoin: Efficacy, toxicity, and dose-serum level relationships in children, The Journal of Pediatrics, Y olo 81, No. S. pp. 995-1002, Nov 1972

53 patients younger than 20 years of age with all types of seizures other than febrile types or petit mal were treated with phenytoin. Clinical control of seizures was obtained in 40 of the 53 patients.

Reviews

1. Nolan SJ et al., Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalised onset tonic-clonic seizures, The Cochrane Library 2013, Issue 1

Phenytoin was compared to phenobarbitone when used as a monotherapy in children (age range, 2 to 16 years) or adults patients (age range, 18 to 81 years) with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types. Data were obtained for 4 of 8 studies meeting the inclusion criteria (n=599) or approximately 63% of the potential data. The main overall results (pooled HR, 95% CI) were (a) time to treatment withdrawal 1.62 (1.23 to 2.14); (b) time to 12-month remission 0.90 (0.69 to 1.18); (c) time to 6-month remission 0.92 (0.73 to 1.16); and (d) time to first seizure 0.85 (0.68 to 1.05). These results indicate a statistically significant clinical advantage for phenytoin in terms of treatment withdrawal. No significant differences for seizure outcomes were found. The authors concluded that the results of this review favor phenytoin over phenobarbitone, as phenobarbitone was significantly more likely to be withdrawn than phenytoin.

2. Friedman MJ et al, Seizures in Children, Pediatr Clin N Am 53 (2006) 257 -277

This is a review of epilepsy in childhood in terms of epidemiology, aetiology, clinical manifestations, diagnosis, differential diagnosis and management. Phenytoin or fosphenytoin is administered in children if a seizure continues despite the use of benzodiazepine. Phenytoin and phenobarbital may be used as second-line agents for persistent seizure activity. Phenytoin is administered IV at a loading dose of 10 to 20 mg/kg, with each 1 mg/kg of drug given, raising the serum concentration by 1 mg/mL. Phenytoin is effective against generalised tonic-clonic and both types of partial seizures. The usual maintenance dose ranges from 4 to 8 mg/kg/day given once, twice, or three times daily. Therapeutic serum levels range from 10 to 20 µg/mL.

MAH3 also cited <u>relevant guidelines identified in the literature:</u>

1. National Institute for Health and Clinical Excellence (NICE). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Jan p.117.

2. Report prepared for World Health Organization October 2006, Phenytoin in Childhood epilepsy, Essential Medicines Application.
3. Kochanek PM, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med 2012 Jan;13(Suppl1): S1-82.
4. Guideline for Management of Children with Epileptic Seizures in British Columbia, April 15, 2011.
5. Diagnosis and management of epilepsies in children and young people. A national clinical guideline. Scottish Intercollegiate Guidelines Network (SIGN) guideline. March 2005.

MAH4:

1. Tudur-Smith C et al, Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic clonic seizures, Cochrane database of Systematic Reviews 2009, Issue 4

Data were available for 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met the inclusion criteria. One important limitation is that in four of the five trials, for people classified as having generalized onset seizures, tonic-clonic seizures were the only seizure types recorded at follow up. Hence results apply only to generalized tonic-clonic seizures. The main overall results were as follows (hazards ratio=HR, HR greater than one indicates a clinical advantage for phenytoin for both remission outcomes and a clinical advantage for valproate for the outcomes time to withdrawal and time to first seizure): (a) time to withdrawal of allocated treatment 1.10 (95% CI 0.79 to 1.54); (b) time to 12 month remission 1.04 (95% CI 0.78 to 1.38); (c) time to six month remission 0.89 (95% CI 0.71 to 1.11) and (d) time to first seizure 0.92 (95% CI 0.74 to 1.14). The results suggest no overall difference between the drugs for these outcomes. No statistical interaction between treatment and seizure type (partial versus generalized) was found. From these five trials one recruited children only (de Silva 1996) and one recruited individuals of all ages (Ramsay 1992).

2. Forsythe I et al, Cognitive impairment in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate, Developmental Medicine and Child Neurology 1991:33;524-34

Randomised, prospective blind study of children allocated to monotherapy with phenytoin, carbamazepine or sodium valproate compared to with controls. 64 Children aged 5-14 years of age who had had a) three tonic clonic seizures, 2) three complex partial seizures or 3) three partial seizures with secondary generalisation. The children were assessed with cognitive tests before medication and three subsequent times over a year. Carbamazepine in moderate dosage adversely affected memory, but sodium valproate and phenytoin did not. After 6 months, memory was better for VPA than CBZ.

3. Thilothammel et al, Comparison of phenobarbitone, phenytoin with sodium valproate: randomized double blind study, Indian Paediatrics 1996 33;549-55

This was a randomised, double-blind clinical trial that recruited 151 paediatric outpatients (4-12 years of age) with generalised tonic-clonic convulsions in a tertiary care hospital (India). Comparison of efficacy and side effects of phenytoin, phenobarbitone or sodium valproate in controlling generalised tonic-clonic seizures was performed. The proportion of children with recurrence did not differ among the 3 groups. More than one side effect was observed in 16 (32%) children on PB, 20(40%) children on PHT and 9(19%) children on SVP and this difference was statistically significant ($p<0.05$). Hyperactivity was the major side effect of PB, observed in 22% of children. Though side effects were more frequent with PHT, most of them disappeared on adjusting drug dosage.

4. De Silva M et al, Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. The Lancet 1996; 347:709-13

This was a randomised, comparative trial of monotherapy (with phenobarbitone, phenytoin, carbamazepine, sodium valproate) in newly diagnosed epilepsy. 167 Children aged 3-16 years of age who had had at least 2 previously untreated tonic-clonic or partial seizures with or without secondary generalisation. 20% of children remained free of seizures and 73% had achieved 1-year remission by 3 years of follow up. No significant differences between the drugs for either measure of efficacy were found.

5. Tudur-Smith C et al, Carbamazepine versus phenytoin monotherapy for epilepsy, Cochrane database of Systematic Reviews 2010, Issue 3

Individual patient data were available for 551 participants from three trials, representing 61% of the participants recruited into the nine trials that met the inclusion criteria. The trials recruited patients with partial onset seizures, or generalized onset tonic-clonic seizures with or without other generalized seizure types. None of the trials collected data on specific generalized seizure types other than generalized tonic-clonic seizures. Only one of the three studies recruited children (de Silva 1996). By convention, for the outcomes time to six and 12month remission hazards ratio (HR) greater than one indicates a clinical advantage for phenytoin, whilst for time to withdrawal and first seizure HR greater than one indicates a clinical advantage for carbamazepine. Results (HRs) were: (i) time to withdrawal of allocated treatment 0.97 (95% CI 0.74 to 1.28); (ii) time to 12 month remission 1.00 (95% CI 0.78 to 1.29); (iii) time to six month remission 1.10 (95% CI 0.87 to 1.39) and (iv) time to first seizure 0.91 (95% CI 0.74 to 1.12). The results suggest no overall difference between carbamazepine and phenytoin for these outcomes.

6. Muller M et al, Oxcarbazepine versus phenytoin monotherapy for epilepsy, Cochrane Database of Systematic reviews 2006

Individual patient data were available for 480 patients from two trials, representing 100% of the patients recruited into the two trials that met our inclusion criteria. One trial recruited children only (Guerreiro 1997). By convention, for the outcomes time to withdrawal of allocated treatment and time to first seizure a hazards ratio (HR) > 1 indicates a clinical advantage for oxcarbazepine and for time to 6 and 12-month remission a HR > 1 indicates a clinical advantage for phenytoin. The main overall results (HR, 95% confidence interval (CI)) were: (i) time to withdrawal of allocated treatment 1.64 (1.09 to 2.47), (ii) time to 6-month remission 0.89 (0.66 to 1.22), (iii) time to 12-month remission 0.92 (0.62 to 1.37), (iv) time to first seizure 1.07 (0.83 to 1.39). The overall results indicate that oxcarbazepine is significantly better than phenytoin for time to treatment withdrawal, but suggest no overall difference between oxcarbazepine and phenytoin for other outcomes. Results stratified by seizure type indicate no significant advantage for either drug for patients with generalized onset seizures, but a potentially important advantage in time to withdrawal for oxcarbazepine for patients with partial onset seizures: HR 1.92 (95% CI 1.17 to 3.16).
The authors considered that the age distribution of adults classified as having generalized epilepsy suggests a significant number of patients may have had their epilepsy misclassified.

7. Guerreiro et al, A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy, Epilepsy Research 1997; 27(2):205-13

The use of oxcarbazepine (OXC) as monotherapy in children and adolescents with newly diagnosed epilepsy was investigated in this double-blind, randomized, parallel-group comparison with phenytoin (PHT). A total of 193 patients aged 5-18 years with either partial onset seizures (PS) or generalised tonic clonic seizures (GTCS) were enrolled. After a retrospective baseline assessment, patients were randomized to OXC or PHT in a 1:1 ratio. The double-blind treatment phase comprised two periods: an 8-week flexible titration period; followed by 48 weeks maintenance treatment. In the efficacy analyses, there were no statistically significant differences between OXC and PHT. Forty-nine (61%) patients in the OXC group and 46 (60%) in the PHT group were seizure-free during the maintenance period. In total, 24 patients in the OXC group discontinued treatment prematurely (two for tolerability reasons) compared

with 34 in the PHT group (14 for tolerability reasons). The number of premature discontinuations due to adverse experiences was statistically significantly lower in the OXC group than in the PHT group. The authors concluded that this trial provides further support for the efficacy and safety of OXC as first-line treatment in children and adolescents with PS and GTCS. In addition, the results show that OXC in these patients has significant advantages over PHT in terms of tolerability and treatment retention.

8. Glauser T et al, Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes Epilepsia: 1–13, 2013

The purpose of this report was to update the 2006 International League against Epilepsy (ILAE) report and identify the level of evidence for long-term efficacy or effectiveness for antiepileptic drugs (AEDs) as initial monotherapy for patients with newly diagnosed or untreated epilepsy. The combined analysis (1940–2012) included a total of 64 RCTs (7 with class I evidence, 2 with class II evidence) and 11 meta-analyses.
The authors stated: "Although ethosuximide and valproic acid have level A efficacy/effectiveness evidence as initial monotherapy for children with absence seizures, there continues to be an alarming lack of well designed, properly conducted epilepsy RCTs for patients with generalized seizures/epilepsies and in children in general. These findings reinforce the need for multicenter, multinational efforts to design, conduct, and analyse future clinically relevant adequately designed RCTs."

Relevant to phenytoin treatment in children the following were identified in the ILAE review:
- *Children with partial-onset seizures*
PHT is possibly (level C) efficacious/ effective as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures
- *Children with generalized-onset tonic–clonic seizures*
PHT is possibly (level C) efficacious/effective for children with newly diagnosed or untreated generalized onset tonic–clonic seizures. Class IV evidence suggests that CBZ and PHT may precipitate or aggravate generalized-onset tonic–clonic seizures (Guerrini et al., 1998; Genton, 2000; Somerville, 2009).
- *Children with absence seizures*
Based solely on scattered reports (class IV), PHT may precipitate or aggravate absence seizures (Guerrini et al., 1998; Genton, 2000; Somerville, 2009).
- *Juvenile myoclonic epilepsy*
Class IV studies indicate that PHT may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic–clonic seizures.

Comments:

PHT is an antiepileptic drug used for the control of partial and generalised tonic clonic seizures.
Due to its safety profile, PHT use has been limited in developed countries as second or third line treatment. Second and third generation AEDs have demonstrated a comparatively safer profile and therefore are used as first line agents for the management of epilepsy in childhood.
PHT remains a highly used AED for neonatal seizures (after phenobarbitone) and in the management of status epilepticus (after benzodiazepines) in children.

The scenario is different in developing countries, where 80% of epileptic people live. PHT is one of the four AEDs on the World Health Organisation (WHO) List of Essential medicines. Specific guidelines for the management of seizures in adults and children have been developed for developing countries where the availability of medicines is restricted (Mental Health Gap Action Programme/Intervention Guide/WHO 2010). According to these guidelines, PHT is recommended in the management of status epilepticus. In addition, if an adult or child has had at least 2 convulsive seizures in the last year on 2 different days, epilepsy should be considered and an AED should be initiated; either phenobarbital, phenytoin, carbamazepine or valproate based on country-specific availability. In children, it is advised to

look for the presence of associated intellectual disability or behavioural problems and if present, consider carbamazepine or valproate (if available) and avoid phenobarbital or phenytoin.

Guidelines for the management of seizures and various epileptic syndromes have been developed by the National Institute for Health and Clinical Excellence *(NICE): "The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care" (2012).*
The guidance states that AED treatment should be individualised according to seizure type, epilepsy syndrome, co-medication and co-morbidity, person's lifestyle and the preferences of the person and their family. PHT is not recommended as first line treatment for any type of seizure or epilepsy syndrome. For focal seizures, PHT should be considered by the tertiary epilepsy specialist only, after a first line AED and adjunctive AEDs have failed. PHT is not mentioned as an option for generalised tonic clonic seizures. PHT, fosphenytoin and/or phenobarbital intravenously are recommended as second line treatments (after IV lorazepam) for the management of prolonged seizures or status epilepticus in hospital.

The Scottish Intercollegiate Guidelines Network issued recommendations for the *"Diagnosis and management of epilepsies in children and young people"* in 2005. PHT is mentioned among a wide range of AEDs that are effective as monotherapy in the treatment of focal seizures. For the management of convulsive status epilepticus the guideline states: "If the seizure has not stopped following administration of a first dose of benzodiazepine, management guidelines have generally suggested repeating this dose followed by a loading dose of phenytoin. Cardiac monitoring is necessary during phenytoin infusion."

Guideline for management of children with epileptic seizures in British Columbia (updated in 2011): This guidance mentions PHT among a list of drugs that have been shown to be effective in children with partial and generalised tonic clonic seizures.

There are not many well designed controlled randomised studies of AEDs in children.
The rapporteur reviewed the studies submitted by the MAHs and also other relevant literature.
The ILAE recommendations state that the primary outcome variable should ideally include assessment of retention after a minimum of 48 week treatment for all seizure types and assessment of efficacy based on a minimum of 24-week seizure freedom for all seizure types.

The EMA guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (2010) also sets specific requirements for therapeutic confirmatory studies. "Pivotal add-on studies should be randomised, double blind, placebo controlled. Monotherapy studies should be randomised, double-blind active controlled trials aiming to demonstrate at least a similar benefit/risk balance of the test product as compared to an acknowledged standard product at its optimal dose. The primary endpoint should be the proportion of patients becoming seizure free for at least 6 months. Overall follow-up should be at least one year, for safety reasons and to verify that the proportion of patients remaining seizure-free is not below the expected rates in this population". Furthermore it is stated that "In children identifying those childhood epilepsy syndromes and types of seizures that may benefit from the drug should be done in large pilot studies including all types of epilepsy syndromes, stratified by syndromes and/or age bands that would provide PK and preliminary efficacy and safety data. Promising results from these studies have to be confirmed by one or more randomised controlled trial for each indication pursued. The pivotal add-on studies should have a randomised, double-blind, placebo-controlled parallel group study design. As more anti-epileptics are approved for the add-on indication, comparative trials may be considered. Efficacy endpoints should be based on the changes in seizure frequency between the treatment maintenance phase and the baseline period."

The MAHs submitted a number of systematic reviews examining the efficacy of PHT compared with other AEDs. PHT was compared in these systematic reviews with: phenobarbitone (Nolan et al.), valproate (Tudur-Smith C.et al.), carbamazepine (Tudur-Smith C.et al.) and oxcarbazepine (Muller M et al.). No significant differences in seizure outcome were found between PHT and valproate and PHT and

carbamazepine. PHT was less likely to be withdrawn compared to phenobarbitone, presumably due to adverse effects. For patients with partial onset seizures, oxcarbazepine was significantly less likely to be withdrawn but current data do not allow a conclusion on whether oxcarbazepine is equivalent, superior or inferior to PHT in terms of seizure control.
The outcomes in these reviews were influenced by both the relative efficacy of the drugs, as well as differences in tolerability and safety.

The authors of the above mentioned reviews highlighted the importance that epilepsy trials are sufficiently powered and well designed to include populations with defined epilepsy syndromes to avoid misclassification. In addition, there is a need to measure longer term outcomes and follow patients up after randomized treatment has been withdrawn.

Some randomised controlled trials in children that were included in these systematic reviews were also submitted by the MAHs (Thilothammal 1996, de Silva 1996, Forsythe 1991 and Guerreiro 1997). In the trial of de Silva comparing PHT with phenobarbitone, participants and personnel were unblinded to treatment allocation; however the investigators suspended randomisation to phenobarbitone due to serious adverse effects after 10 children had been randomised to the drug. Thilothammal et al. found phenobarbitone, PHT and valproate were equally effective in controlling generalised tonic clonic seizures. The most frequent side effects were observed with PHT but most of them disappeared after dose adjustment.
Another randomised double blind controlled study (Canadian Study group for childhood epilepsy, 1998) found that clobazam had equal effectiveness with carbamazepine and PHT as monotherapy for partial, partial with secondary generalisation or primary generalised tonic clonic seizures.
A randomised prospective study by Callaghan N et al (1985) aimed to compare the efficacy of PHT to carbamazepine and sodium valproate as monotherapy in recently diagnosed patients and the authors concluded that all three drugs were highly effective in the control of generalised seizures but less effective for partial seizures. Interestingly, excellent or good control in patients taking PHT was achieved with sub-therapeutic blood levels. The study included adults and children, however neither the number and ages of children were mentioned nor were the results of the study reported separately for children. Allocation concealment, blinding and power calculation were also not mentioned.
The remaining submitted studies which examined the efficacy of phenytoin in children had major limitations in their methodology which make it difficult to draw valid conclusions. Such limitations were: retrospective studies, uncontrolled, unblinded, absence of randomisation, allocation concealment not mentioned, mixed studies including adults and children without specifying the number and age groups of children or without reporting results separately for children, unspecified subgroups by seizure type, inadequate follow up, not clearly defined primary endpoints, no clear definition of inadequate control of seizures, results confounded by co-administration of other AEDs, not clearly defined timing of assessments, no detailed description of frequency and type of adverse effects and not well described power calculation or not described at all.
Despite the methodological limitations, there is some evidence from uncontrolled prospective or retrospective studies (Abernathy RS, 1966, Sicca et al, 2000, Borofsky RG et al, 1972) that phenytoin is an efficacious AED but at the cost of a high frequency of observed side effects.

MAH1 submitted 3 old studies. Although of low methodological quality, these studies provided some early evidence on the efficacy of PHT. The study by Grinschgl G.et al (1952) suggested that PHT is efficacious in petit mal (absence) seizures. However, it is currently known that PHT should not be used to treat absence seizures, as it is not only ineffective but may also exacerbate this type of seizures. According to the NICE guidelines, "if there are absence or myoclonic seizures or if juvenile myoclonic epilepsy (JME) is suspected, PHT should not be offered, as it might worsen the seizures." The British Columbia guidelines also state: "PHT might increase the seizure frequency in childhood and juvenile absence epilepsy and JME." These guidelines are supported by published reviews and papers examining drugs that aggravate epilepsy (Genton P, 2000, Perucca E et al, 1998, Osorio I et al, 2000). The ILAE updated

evidence review (Glauser T et al, 2013) also states: "Class IV (Non randomised, prospective, controlled or uncontrolled studies, case series, or expert reports) studies indicate that PHT may precipitate or aggravate absence seizures, myoclonic seizures, and in some cases generalized tonic–clonic seizures."

It is noted that the SmPC of phenytoin in section 4.4 "Special warnings and precautions for use" states: "Phenytoin is not effective for absence seizures". However, a warning that phenytoin may aggravate this type of seizures does not exist. The rapporteur is of the view that such a warning should be included. The rapporteur proposes the following wording to be included in section 4.4: "PHT may precipitate or aggravate absence seizures and myoclonic seizures".

Status epilepticus:
All guidelines identified (NICE, British Columbia, SIGN) recommend the intravenous use of phenytoin for the management of seizures that persist after 2 doses of benzodiazepines (lorazepam or diazepam or midazolam). The same regimen was used in studies submitted by the MAHs (Hussain N et al, 2007, Koul R, 2002, Brevoord J et al, 2005).

Neonatal seizures:
Data were submitted supporting the use of PHT in neonates with seizures. In these papers (Bartha AI et al, 2007, Castro C et al, 2005, McBride MC et al, 2000), PHT was used most commonly following phenobarbital failure to control the seizures. Although it is known that seizures in the neonatal period are associated with worse neurodevelopmental outcomes later in childhood, the efficacy of drugs to prevent this has not been proven. A Cohrane review assessing different anticonvulsants for the treatment of neonatal seizures (Booth D, Evans DJ, 2009) concluded that further randomised trials of sufficient size are needed to evaluate important long term outcomes, such as mortality and severe neurodevelopmental delay. The World Health Organization (2011 Guidelines on Neonatal seizures) recommends: "In neonates who continue to have seizures despite the administering of the maximal tolerated dose of phenobarbital, either a benzodiazepine or phenytoin or lidocaine may be used as the second-line agent for control of seizures, the use of phenytoin or lidocaine requiring cardiac monitoring facilities (weak recommendation)"
Painter et al (1999) compared phenobarbital against PHT in 59 neonates. The drugs were similarly but incompletely effective, as seizures were controlled with either drug alone in less than half of the neonates. The authors concluded that effective treatments for neonates are an important priority for future research. Scher MS et al (2003) also found that phenobarbital and PHT resulted in equal rates of uncoupling in neonates, i.e. the persistence of electrographic seizures without a clinical expression. The authors proposed that the quantification of seizures and the preferred endpoint for AED efficacy in neonates should be by EEG monitoring rather than suppression of clinical seizures.

Febrile seizures:
One review (Offringa M, 2012) was submitted on the prophylactic management for febrile seizures in children. No long term benefit was found for the intermittent use of several AEDs, including PHT, in terms of reducing the risk of developing epilepsy. However, a significant prevalence of adverse effects was noted. The authors did not advocate for the use of AEDs for the management of febrile seizures. Although prophylaxis for febrile seizures has been suggested by some authors in the past (Bacon, 1981), the American Academy of Paediatrics ("Febrile Seizures: Clinical Practice Guideline for the Long-term Management of the Child With Simple Febrile Seizures." AAP, 2008) and the Scottish Intercollegiate guidelines network (SIGN, 2005) recommend that children with febrile seizures should not be treated prophylactically with antiepileptic drugs. The SIGN guideline states: "children with febrile seizures, even if recurrent, should not be treated prophylactically with antiepileptic drugs. While phenobarbital and sodium valproate may reduce recurrence rates, the risk of adverse effects does not justify their routine use. They do not influence the risk of subsequent developing epilepsy."

Traumatic brain injury/seizure prophylaxis:
The study by Young et al (2004) did not find an effect of PHT in reducing early post-traumatic seizures in

children with moderate and severe brain injury. However, this study had a small sample size and unclear criteria for randomisation.
Kochanek PM et al published in 2012 *guidelines for the acute management of severe traumatic brain injury (TBI) in infants, children, and adolescents (second edition).* According to these, prophylactic treatment with PHT may be considered to reduce the incidence of early posttraumatic seizures (PTS) in paediatric patients with severe TBI (the strength of recommendation is weak). However, there is no evidence that such treatment reduces the long term risk of PTS or improves long term neurologic outcome. The use of PHT in these guidelines was based in a retrospective cohort study by Lewis et al (1993). In this study PHT reduced post traumatic seizures in paediatric patients with a low Glasgow Coma Score. However, the rapporteur would like to note that the patients in this study were not randomly assigned to treatment with PHT or no treatment and it should be considered that the decision to treat or not could have been influenced by other factors that also affect the outcome/risk of posttraumatic seizures.
Free unbound PHT concentrations may be high in trauma patients because of low albumin and this could be associated with a higher rate of side effects at normal "therapeutic" concentrations (Bauer et al, 1983). Children with severe neurotrauma were also found to have altered PHT metabolism. Rapid inhibition of metabolism was observed initially, followed by induction of metabolism, which was approximately two-fold higher than reported values for non-stressed children (Stowe et al, 2000). Wolf GK et al (2006) proposed that free PHT concentrations should be routinely measured in critically ill children to prevent possible intoxications and ensure therapeutic dosing.

In conclusion, the rapporteur agrees with the MAHs that PHT is an efficacious antiepileptic drug for the management of certain types of seizures (partial-onset and generalised-onset tonic clonic) in childhood despite the fact that its use has been limited in developed countries based on its adverse safety profile and the development of newer safer medicines. PHT remains a highly used AED worldwide although its place in the chronic management of epilepsy in children (and adults) differs substantially between the developing and developed countries.
No new data were identified regarding the efficacy of phenytoin in childhood epilepsy. However, the rapporteur is of the view that a warning should be included in section 4.4 of the SmPC: "PHT may precipitate or aggravate absence seizures and myoclonic seizures".

Posology

MAH3 (current SmPC of brand leader)

Phenytoin sodium oral suspension, capsules and tablets

4.2. Posology and Method of Administration
Paediatric Dosage
For oral tablets or capsules initially, 5 mg/kg/day in two or three equally divided doses with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old and adolescents may require the minimum adult dose (300 mg/day). If the daily dosage cannot be divided equally, the larger dose should be given at bedtime.
For the oral suspension initially, 5 mg/kg/day in two or three equally divided doses with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years and adolescents may require the minimum adult dose (300 mg/day).

Phenytoin sodium injection

4.2. Posology and Method of Administration

Infusion Administration: For administration by infusion, parenteral phenytoin should be diluted in 50-100 mL of normal saline with the final concentration of phenytoin in the solution not exceeding 10 mg/mL. Administration should commence immediately after the mixture has been prepared and must be completed within one hour (the infusion mixture should not be refrigerated). An in-line filter (0.22-0.50 microns) should be used. Each injection of intravenous phenytoin should be preceded by a saline flush and followed by an injection of sterile saline through the same needle or intravenous catheter to help reduce local venous irritation due to the alkalinity of the solution.
Dosage is not to exceed 50 mg/minute, intravenously in adults, and not to exceed 1-3 mg/kg/minute in neonates and children. There is a relatively small margin between full therapeutic effect and minimally toxic doses of this drug (see Section 4.4 Special warnings and precautions for use – General).
Status Epilepticus: In adults, a loading dose of 10 to 15 mg/kg should be administered slowly intravenously, at a rate not exceeding 50 mg per minute (this will require approximately 20 minutes in a 70 kg patient). The loading dose should be followed by a maintenance dose of 100 mg orally or intravenously every 6-8 hours. Absorption of phenytoin in neonates and children may be unreliable after oral administration. A loading dose of 15-20 mg/kg of phenytoin intravenously will usually produce serum concentrations of phenytoin within the generally accepted therapeutic range (10-20 μg/mL). The drug should be injected slowly intravenously at a rate not exceeding 1-3 mg/kg/minute.

Comments:

There is an abundance of pharmacokinetic data for phenytoin in children as already discussed in section IV3 1.a. The paediatric doses used in the submitted studies are in line with the posology given in the SmPCs. BNF for children and the World Health Organisation also give posology that is in line with the posology given in the SmPCs.
It is important to note that the dose should be individualised based on blood level monitoring as the relationship between dose and blood levels is not always predictable. The SmPCs contain adequate information to cover this aspect and guide dosing in children.
The rapporteur considers that no change in the posology of PHT in children is needed.

Other indications

1. Trigeminal neuralgia as second line if carbamazepine is ineffective

The MAHs did not submit any data regarding this indication in the paediatric population.

Comments:

Trigeminal neuralgia (TN) is a rare disorder in childhood. Phenytoin was the first drug that was reported to be effective in preventing pain paroxysms. Currently, carbamazepine is considered the first line treatment. Other AEDs including PHT, baclofen and gabapentin have been used as second line treatments. In one study proposing an evidence-based algorithm for the management of TN, second line therapy is either oxcarbamazepine or combination of carbamazepine and lamotrigine or baclofen (Jorns TP, 2007). Multiple neurosurgical interventions are also used for treating TN, such as microvascular decompression, percutaneous rhizotomy, stereotactic radiosurgery and other (Nurmikko TJ, 2001). PHT appears to be the least studied drug for this condition and it is not a preferred second line agent. The rapporteur did not identify any randomised controlled trials for the efficacy of PHT in this indication. Some case reports of trigeminal neuralgia in children exist but only two publications where PHT was used were identified (Okada R et al, 1962 and Lopes PG et al, 2002).

2. Cardiac arrhythmias when first line therapy is ineffective

The MAHs did not submit any data regarding this indication in the paediatric population.

Comments:

Phenytoin has class IB antiarrhythmic properties.
There are published reports of paediatric cases were PHT was used successfully to treat ventricular arrhythmias (Kavey RE et al, 1982, Garson A Jr et al, 1980, Garson A Jr et al, 1985).

The case of a newborn with persistent ventricular tachycardia, resistant to esmolol and amiodarone, that eventually responded to PHT therapy was also reported by Sun et al. (2011). The authors concluded that PHT still has a place in the treatment options for neonates and infants who are resistant to the most commonly used antiarrhythmic regimens.
A recent (2013) consensus statement from the European Heart Rhythm Association (EHRA) and the Association for European Paediatric and Congenital Cardiology (AEPC)-Arrhythmia Working Group for the management of arrhythmias in children does not mention phenytoin as a therapeutic option for any type of arrhythmia. Regarding class IB agents the consensus states: "Class IB agents (lidocaine and mexiletine) are mostly effective in myocardial ischaemia and rarely used in children."

Another recent paper (Hanash CR, 2010) reviewing the emergency diagnosis of arrhythmias in children also does not mention phenytoin.

Based on the published literature, it appears that the use of PHT in the management of cardiac arrtythmias in children has decreased significantly in recent decades and other agents are preferred. However, there are reports of its use in the paediatric population in refractory arrhythmias and probably there is a place for its use when standard antiarrhythmic agents are ineffective.

c. Safety

MAH1:

The MAH stated that an important aspect regarding the safety of PHT in children was revealed in recent literature (see below, Arya R et al, 2011). Oral folic acid supplementation (0.5 mg/day) was found to decrease the incidence of phenytoin-induced gingival overgrowth in children with epilepsy aged 6–15 years on PHT monotherapy. The MAH considered that this finding has the potential to facilitate the proper use of PHT in this patient group. However, the MAH did not propose any changes in the SmPC regarding the prophylactic use of folic acid for the prevention of gingival hyperplasia.

Arya R. et al, Folic acid supplementation prevents phenytoin-induced gingival overgrowth in children, Neurology 76 April 12, 2011

A randomized, double-blind, placebo-controlled trial was conducted at a tertiary level hospital from May 2008 to June 2009. Children aged 6–15 years started on PHT monotherapy within the last 1 month were eligible for inclusion. Preexisting gingival overgrowth, use of other folic acid antagonists, and macrocytic anemia were exclusion criteria. Trial subjects were randomized to receive either folic acid (0.5mg/day) or placebo. The primary outcome measure was incidence of any degree of gingival overgrowth after 6 months of PHT monotherapy.
A total of 120 children were recruited, 62 and 58, respectively, in folic acid and placebo arms. The 2 arms were comparable at baseline. Twenty-one percent of patients in the folic acid arm developed PIGO, as compared with 88% receiving placebo ($p < 0.001$). Absolute risk reduction of PIGO by folic acid was 67% (95% confidence interval 54%–80%), and relative risk reduction was 0.76. Oral folic acid was found

to decrease the incidence of PIGO in children on PHT monotherapy, in a statistically significant and clinically relevant manner. The authors concluded that this study provides Class I evidence that folic acid supplementation, 0.5 mg/day, is associated with prevention of gingival overgrowth in children taking PHT monotherapy.

MAH1 also submitted all periodic safety update reports (PSURs) on their PHT product (from 13 March 1958 to 15 May 2012). Line-listings for adverse reactions (up to 08 May 2013), for which a possible connection with PHT could not be definitely excluded, were reviewed for reports on paediatric patients. The MAH stated that the very low incidence of reported adverse reactions in children compared with a considerable patient exposure indicates that PHT is a medicinal product suitable and safe for use in children and therefore no changes in the SmPC are necessary.

MAH2:

1. Wilson JT. et al, High incidence of a concentration-dependent skin reaction in children treated with phenytoin. Br Med J. 1978 Jun 17;1(6127):1583-6

A particularly high incidence of rash was seen in children with epilepsy treated with phenytoin. Ten children with untreated epilepsy were therefore included in a prospective study and given either 3 (group 1) or 6 (group 2) mg of phenytoin/kg body weight/day for five days followed by 6 mg/kg body weight/day for both groups. Four of the five children in group 2 compared with only one of the five in group 1 developed a rash seven to 12 days after the start of treatment. Patients with rashes had significantly higher plasma phenytoin concentrations. Whenever the phenytoin concentration was higher than 14 micromol/l on day 5 a rash occurred. The authors concluded that these findings indicate that the generalised skin reaction is caused by a high body burden of phenytoin, which results from either a high load of the drug or a low clearance rate.

2. Aldenkamp A.P et al., Withdrawal of Antiepileptic medication in children-effects on cognitive function: the multicentre Holmfrid study, Jan 1993, Neurology 43

This was an open, controlled, non-randomised study of 100 children 7-18 years diagnosed with epilepsy who were seizure free for more than 1 year and still on monotherapy of AED. Each child was matched with a healthy classmate and performed neuropsychological testing and EEG before and after 3-4 months of complete withdrawal of the AED. 83 patients were assessed (56 on carbamazepine, 17 on valproic acid and 10 on phenytoin). Significant improvement attributable to drug withdrawal was found on only one of the cognitive tests, namely the psychomotor speed. Group differences between the epilepsy group and the control group at baseline were found, that persisted after drug withdrawal. The authors concluded that this study provided some evidence that phenytoin may have a different cognitive profile than carbamazepine with more impairment on tests that measure motor and mental speed.

3. Aman M.G., Effects of Phenytoin on Cognitive-Motor Performance in Children as a Function of Drug Concentration, Seizure Type and Time of Medication, Epilepsia, 35(1):172-180, 1994

Fifty children with well-controlled seizures who were receiving phenytoin (PHT) monotherapy were tested three times at weekly intervals on a cognitive-motor test battery. The first assessment served as a practice session, and PHT was given either before or withheld until after testing to create peak and trough concentrations, respectively, in the second and third sessions. On average, PHT levels as measured in saliva were in the low therapeutic range. The experimental condition (PHT before or after test sessions) was randomized and balanced across subjects, and assessments were made with examiners blind to diagnosis and timing of PHT ingestion. A variety of statistical models was used to analyse for the effect of age, diagnosis (partial vs. generalized epilepsy), PHT order, PHT concentration (as measured in saliva), and trough/peak concentration effects. Greater age was consistently associated with better performance,

but diagnosis, PHT concentration levels, and transition from trough to peak concentration days had few discernible effects on psychomotor performance. Thus, fluctuations in PHT, of the order of 50%, appear to have no or immeasurably small effects in children with well-controlled seizures receiving monotherapy in low therapeutic dosages.

4. Bacon C.J. et al, Behavioural effects of phenobarbitone and phenytoin in small children, Arch Dis Child 1981;56:836-840

Mothers of 56 children under 2 years old taking phenobarbitone and mothers of 55 children taking phenytoin recorded on questionnaires changes they had noted in the children's behaviour 3 and 9 weeks after starting the drug. Severe behavioural disturbance was noted by many, but the pattern and incidence was similar to that recorded by the mothers of 50 children starting a placebo, and the authors attributed the disturbance to the effect of a recent hospital admission (after first febrile convulsion). There was a small improvement in the behaviour of 20% of children who had been taking phenobarbitone for a year when they stopped it, but in this age group the disturbance caused by phenobarbitone did not appear to be significant.

5. Bawden H.N. et al, The cognitive and behavioural effects of clobazam and standard monotherapy are comparable. Canadian Study Group for Childhood Epilepsy, Epilepsy Res. 1999 Feb;33(2-3):133-43

A randomized, double-blind, prospective study was carried out at three Canadian pediatric epilepsy centres. This study was part of a larger multi-centre study on the efficacy of clobazam. Children with newly diagnosed epilepsy were assigned randomly to receive clobazam or carbamazepine. Children who had failed previous treatment with carbamazepine were assigned randomly to clobazam or phenytoin. Children who had failed on any other antiepileptic drug were assigned randomly to receive clobazam or carbamazepine. In a subset of patients neuropsychological assessments were carried out at 6 weeks and 12 months after initiation of medication. Intelligence, memory, attention, psychomotor speed, and impulsivity were assessed.
There were no differences between the clobazam and standard monotherapy groups on any of the neuropsychological measures obtained at 6 weeks or 12 months. There was no evidence for deterioration in performance for those children who remained on clobazam for the entire 12-month study period.
The authors concluded that the cognitive and behavioural effects of clobazam appear to be similar to those of standard monotherapy.

6. Berg I. et al, Psychiatric aspects of epilepsy in childhood treated with carbamazepine, phenytoin or sodium valproate: A random trial. Developmental Medicine & Child Neurology, 35: 149–157, 1993

Sixty-four new cases of childhood epilepsy were randomly assigned to either carbamazepine, phenytoin or sodium valproate, and were assessed with behavioural checklists before medication and after one and six months of treatment. Those treated with carbamazepine and sodium valproate had minor behavioural difficulties after a month of treatment, but these did not persist. Mothers of the epileptic children had unusually high levels of anxiety and depression two months, on average, after epilepsy was diagnosed.

7. Blennow G. et al, Discontinuation of antiepileptic drugs in children who have outgrown epilepsy: effects on cognitive function, Epilepsia. 1990;31 Suppl 4:S50-3

Cognitive function is frequently impaired in children with epilepsy, compared with age-matched controls. It can be difficult to evaluate the significance of various contributory factors. The effects of antiepileptic drugs may be studied in children who have outgrown their epilepsy but are still being treated. A multicenter study to assess various aspects of cognitive function in children with different forms of epilepsy, both during and after treatment with antiepileptic drugs, is currently under way. Definitive results are not yet available; interim analysis of the findings suggests that short-term memory is decreased

in all subgroups of children being treated for epilepsy, compared to controls. In this study 6 children are treated with phenytoin.

8. Chung S., Ahn C., Effects of anti-epileptic drug therapy on bone mineral density in ambulatory epileptic children. Brain Dev. 1994 Sep-Oct;16(5):382-5.

In order to assess the bone changes in the subjects receiving anti-epileptic drugs (AEDs), bone mineral densities (BMDs) of the arms, legs, ribs, pelvis, spine, and the whole body were scanned in 78 epileptic children and in 78 controls using dual photon absorptiometry. The study subjects were classified according to the duration of the monotherapy with phenobarbital (PB) or phenytoin (PHT); those who received AEDs for less than 12 months as Group I, for 13-23 months as Group II, and for 24 months as Group III. Group III was subclassified according to the kind of AEDs administered, into those receiving PB as Group IIIp, and those receiving PHT as Group IIId. There was no significant differences in the BMDs of each area, when compared to each control in Groups I and II. In Group III, there were significant differences in ribs and spine, according to the duration of administration. In Group IIIp, there was a significant difference in ribs and spine, and, in Group IIId, there was a significant difference in most of the areas. The authors concluded that the measurement of BMDs in the ribs and spine is necessary for the early detection of subtle bone loss and recommended that vitamin D should be administered to children with epilepsy receiving AEDs over 24 months.

9. Gonzalez-Martin G. et al, Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study, Int J Clin Pharmacol Ther. 1998 Oct;36(10):530-3

The aim of this study was to determine the frequency and the characteristics of ADRs in 219 hospitalized pediatric patients, using an intensive and prospective drug surveillance method. The frequency of ADRs in these patients was 13.7%. The systems most commonly affected were the gastrointestinal (32.5%), the central nervous (20.0%), and the metabolic systems (17.5%). Asparaginase, methotrexate, phenytoin, phenobarbital, erythromycin, and salbutamol were probably the drugs associated with the ADRs. According to causality, 54.2% of the ADRs were regarded as probable, and 32.2% as possible. The majority of the ADRs were moderate (51.2%), 27.9% were severe. The main treatment of the ADRs was the withdrawal of the suspected drugs. The length of the stay in the hospital and the total number of drugs given to the patients influenced significantly the frequency of ADRs. 93% of the ADRs were dose-dependent.

10. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM. The teratogenicity of anticonvulsant drugs. N Engl J Med2001;344:1132–8.

In this study 128,049 pregnant women were screened at delivery to identify three groups of infants: those exposed to anticonvulsant drugs, those unexposed to anticonvulsant drugs but with a maternal history of seizures, and those unexposed to anticonvulsant drugs with no maternal history of seizures (control group). The infants were examined systematically for the presence of major malformations, signs of hypoplasia of the midface and fingers, microcephaly, and small body size. The combined frequency of anticonvulsant embryopathy was higher in 223 infants exposed to one anticonvulsant drug than in 508 control infants (20.6 % vs. 8.5 %; odds ratio, 2.8; 95 percent confidence interval, 1.1 to 9.7). The frequency was also higher in 93 infants exposed to two or more anticonvulsant drugs than in the controls (28.0 percent vs. 8.5 percent; odds ratio, 4.2; 95 percent confidence interval, 1.1 to 5.1). The 98 infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during the pregnancy did not have a higher frequency of those abnormalities than the control infants. The authors concluded that a distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself.

11. KIni U. et al, Dysmorphic features: an important clue to the diagnosis and severity of fetal anticonvulsant syndromes, Arch. Dis. Child. Fetal Neonatal Ed. 2006 ;91;90-95

This was a retrospective study of 375 children born to 219 mothers with epilepsy. The age of the study group ranged from 6 months to 16 years. Each child underwent a physical examination and a battery of neuropsychological tests. Dysmorphic features were scored from photographs on a blind basis by a panel of dysmorphologists.
A total of 274 children were exposed to AEDs (63 to valproate, 94 to carbamazepine, 26 to phenytoin, 15 to other monotherapies, and 76 to polytherapy). Major malformations were identified in 14% of children exposed to valproate in utero, 5% exposed to carbamazepine, and 4% in the non-exposed group. Overall, 47% of exposed children were correctly identified as having been exposed to AEDs in utero. There was a significant correlation between verbal intelligence quotient and dysmorphic facial features in the valproate exposed children only.
Children exposed to valproate have more distinctive facial features, but a subtle and distinctive facial phenotype is also seen in children exposed to carbamazepine. Nearly half (45%) of unexposed children had some of the facial features associated with AED exposure, showing that many of these features may be seen as part of normal variation and that the diagnosis of the fetal anticonvulsant syndrome is difficult to make on the basis of facial gestalt alone. The authors considered that Developmental surveillance should be offered to children with prenatal exposure to AEDs, particularly those with exposure to high doses of valproate.

12. Koch S. et al, Antiepileptic drug treatment in pregnancy: drug side effects in the neonate and neurological outcome. Acta Paediatr. 1996 Jun;85(6):739-46

This study examined the relationship between the maternal antiepileptic therapy, neonatal behaviour and later neurological functions in infancy. The study comprised 40 children exposed in utero to a single antiepileptic drug (phenobarbitone, phenytoin, valproic acid). Valproic-acid-exposed children were the highest compromised, except for apathy, which was most profound in phenobarbitone-exposed neonates. Valproic acid serum concentrations at birth correlated with the degree of neonatal hyper-excitability and neurological dysfunction when children were re-examined 6 years later. The authors suggest that valproic acid may not only cause malformations but also cerebral dysfunction immediate and long term. Phenytoin exposed neonates showed few signs of disturbed neurobehaviour.

13. Prasad VN. et al, Folic Acid and Phenytoin Induced Gingival Overgrowth - Is There A Preventive Effect, J Indian Soc Pedo Prev Dent June (2004) 22 (2) 82-91

The role of folic acid (5mg/day) in combination with oral hygiene measures (group II) vis-a-vis oral hygiene measures alone (group I) in prevention of phenytoin-induced gingival overgrowth was investigated in a one-year follow-up study on sixty, 8-13-year-old epileptic children receiving phenytoin. The allocation of the children to the two groups was done alternately. In these children, at baseline, plaque, gingivitis and probing depths of gingival sulcus were recorded. These parameters were reevaluated at 3-monthly intervals when gingival overgrowth was also recorded. After a period of one year, gingival overgrowth occurred in 60 and 50 percent children of groups I & II respectively and its development, too, was delayed in group II. More cases (93 percent) in group II exhibited minimal overgrowth as against 78 percent in group I. The study concluded that systemic folic acid prescribed along with phenytoin delays the onset and reduces the incidence and severity of gingival overgrowth induced by phenytoin. The benefit of systemic folic acid, though evident clinically was not found to be statistically significant.

14. Tonnby B. et al, Withdrawal of antiepileptic medication in children. Correlation of cognitive function and plasma concentration--the multicentre 'Holmfrid' study, Epilepsy research 19 (1994) 141-152

Eighty-three patients with epilepsy and 83 matched controls completed 12 computerized cognitive tests while on antiepileptic drugs and six months later when they had been medication-free for three to four months. All patients had been seizure-free for more than one year and were on monotherapy with carbamazepine (CBZ, n = 56), valproate (VPA, n = 17), or phenytoin (PHT, n = 10). The tests and plasma concentration collection were done at noon. The mean peak plasma concentrations in the CBZ patients were as follows: 31% below 30 mumol/l, 48% between 30 and 42 mumol/l and 21% above 42 mumol/l. No difference in performance could be detected between the groups. One significant correlation between plasma concentration and test results was found. The mean VPA concentration was 625 mumol/l (S.D. 189). A tendency towards a weak negative correlation between test results and plasma concentration was present. The PHT patients' therapeutic range had a mean concentration of 32.0 mumol/l (S.D. 18.5). One significant correlation between a memory test and plasma concentration could be detected. Overall, the patients in the different antiepileptic groups performed less good than the control group and in a few cases the differences were statistically significant when compared either before or after withdrawal. A comparison of the changes after withdrawal showed improvement in the majority of tests, but these changes were also present in the matched control group.

MAH2 also submitted PSUR data covering the period 2/1/2009 to 1/1/2012. No new paediatric safety concerns were identified during this period and the MAH concluded that no update of the SmPC is deemed necessary.

MAH3:

A cumulative search of the biomedical literature through 30 April 2013 was performed for phenytoin use in the paediatric population. A total of 652 literature articles were retrieved and reviewed. The vast majority of the literature articles reviewed involved cases or data concerning intrauterine exposure, were single case reports, or were discussions of events which are listed in the CDS for phenytoin. The literature articles concerning listed events were reviewed and the MAH concluded that the clinical course and outcomes in the paediatric population are consistent with those in the adult population.

The MAH presented two publications describing unlisted adverse events:

1. Korinthenberg R, Theyhrle L, Zimmerhackl LB. Renal tubular dysfunction following treatment with anti-epileptic drugs. European Journal of Pediatrics. 1994;153(11):855-8

This study evaluated renal side-effects of anti-epileptic medication in 59 children, by performing a cross-sectional study of various aspects of renal function. The patients had been on anti-epileptic monotherapy for at least 3 months. None had a history of renal disease. Twenty three healthy children of the same age group served as controls. After collecting 24-hour urine samples, glomerular function was derived from creatinine clearance and from the excretion of albumin. Proximal tubular function was investigated by the urinary excretion of alpha 1-microglobulin and of the tubular enzymes N-acetyl-beta-D-glucosaminidase, alanine-amino-peptidase, and fructose-1,6-di-phosphatase. Distal tubular function was examined by the 24-hour excretion of Tamm-Horsfall protein. On treatment with carbamazepine (n = 27) and phenytoin (n = 8), the excretion of alpha 1-microglobulin was significantly increased, as compared with the healthy controls. On valproate (n = 20), ethosuximide (n = 9), and phenytoin (n = 8), therapies significantly increased excretion of N-acetyl-beta-D-glucosaminidase. The authors interpreted this as an indication of a functional disturbance of the proximal tubulus. The other parameters, indicating function of the glomerulus, loop of Henle and distal tubules did not differ from normal. The authors concluded that patients on anti-epileptic treatment with therapeutic drug levels may demonstrate minor signs of tubular dysfunction. The authors consider that these are probably insignificant from a clinical standpoint but they should be considered in drug overdose.

2. Saito Y, Oguni H, Awaya Y, et al, Phenytoin-induced choreoathetosis in patients with severe myoclonic epilepsy in infancy. Neuropediatrics 2001;32(5):231-5

This paper described 3 patients with severe myoclonic epilepsy (SME) in infancy who suffered from choreoathetosis as an adverse effect of phenytoin. Choreoathetosis appeared when these patients were 8, 19, and 21 years old, 2 days to 6 months after increasing the phenytoin dosage. Choreoathetosis disappeared when the phenytoin dosage was decreased. The 2 older patients experienced episodic and rather paroxysmal onset of long-lasting choreoathetosis, requiring the differential diagnosis from degenerative disease.
In 1 of the patients, an ictal single-photon emission computed tomography (SPECT) revealed decreased perfusion in the basal ganglia contralateral to the unilateral choreoathetosis. Polypharmacy, including carbamazepine and zonisamide, may have facilitated the onset of choreoathetosis. The authors concluded that: "Phenytoin-induced choreoathetosis in the patients with SME is an important differential diagnosis among degenerative disorders involving involuntary movements. The episodic and paroxysmal nature of this movement disorder can delay its diagnosis and effective treatment. Patients with SME appear to be particularly vulnerable to this side effect of phenytoin, indicating the possible involvement of basal ganglia in the pathophysiology of this type of epilepsy."

The MAH reviewed these two articles and concluded that they do not represent a new safety signal. However, the MAH will continue to monitor cases of choreoathetosis during routine pharmacovigilance activities. The MAH concluded that, based on a cumulative review of the literature in paediatric patients administered phenytoin, no new safety signals were identified and no changes to the CDS are recommended.

MAH3 also reviewed post-marketing phenytoin paediatric cases. The MAH's safety database contains cases of adverse events reported spontaneously to the MAH, cases reported by the health authorities, cases published in the medical literature, cases from MAH-sponsored marketing programs, and cases of serious adverse events reported from clinical studies regardless of causality.
A total of 1242 cases reporting 3384 adverse events were identified meeting the search criteria for paediatric phenytoin reports.
Among the 1242 paediatric cases identified by the search, there were 68 (5.5%) reports of death in infants, children, or adolescents who received phenytoin. The paediatric cases with a fatal outcome were presented in detail. The MAH concluded that the causes of death reported in paediatric phenytoin patients are consistent with what would be expected in this patient population. The events occurring most frequently are adequately described in the CDS. On the basis of this review, no changes to the CDS are warranted regarding fatal events in children.

Phenytoin PSURs from 5 periods that covered the dates from 01 August 1998 through 31 January 2012 were reviewed. Review of the cases during the 5 periods did not identify any paediatric safety concerns with phenytoin and thus no changes are recommended by the MAH to the CDS.

MAH4:

A cumulative and qualitative safety data review (from PSUR data) relevant to all phenytoin cases stored in the Recordati safety database to 03 May 2013 and focused on the paediatric population has been performed. No new safety concern or signals have been identified and the MAH concluded that no changes in the SmPC are deemed necessary.

Comments:

The MAHs concluded that no new safety data were identified that would impact on the products' benefit: risk assessment.

A UK study (Clarkson A. 2002), examining the suspected ADRs associated with fatal outcomes in

children utilising the yellow card scheme, found that AEDs were associated with the greatest number of reports of fatalities and hepatotoxicity in particular.
Among anticonvulsants, PHT is a drug with well-known potential adverse effects in both adults and children. Its safety profile has limited its use in developed countries to a second line agent for the chronic management of epilepsy.
Adverse effects of PHT can be dose-related or idiosyncratic, acute or chronic. Well described adverse effects of phenytoin are: serious skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), drug rash with eosinophilia and systemic symptoms (DRESS), CNS effects such as nystagmus, ataxia, slurred speech and decreased coordination, haematopoietic complications, liver function impairment, hypertrichosis, gingival hyperplasia and other.

The MAHs submitted PSUR data as well as evidence from the available literature describing adverse events of PHT in the paediatric population.

The MAHs submitted published data covering the following safety issues:

Effects on cognitive function:
Most AEDs have been implicated to potentially negatively affect cognitive function. Cognitive impairment in children with epilepsy can be due to many factors, such as the neuropathology underlying the epilepsy, seizures, epileptiform activity, psychosocial problems and AED effects (Bourgeois BF, 2004).
A recent review on the cognitive effects of AEDs (Ijff et al, 2013) in children concluded: "Phenytoin may have an impact on cognitive function, specifically on mental speed, but this effect seems only clinically relevant in higher dosing and in polytherapy. Moderate doses of monotherapy do not seem to induce much of an effect. These effects are similar in adults and in children."
Most studies employ a wide range of assessments in order to examine different aspects of cognition. Eddy et al (2011) conducted a review for the cognitive impact of antiepileptic drugs. It is mentioned in this review that PHT has been implicated in declines of concentration, memory, visuomotor functions and mental speed. However, it was concluded in the review that it is difficult to compare findings across studies owing to the variation in study design, treatment group and assessment tools. Effects on cognition following PHT use were also reported in the MAHs' submitted studies; Aldenkamp et al. (1993) found that children had slowed performance on information processing tasks with phenytoin in comparison to carbamazepine. Tonnby et al and Blennow et al found effects on memory with PHT treatment. On the other hand, Aman MG et al (1994) found that day to day variation in PHT concentration levels did not have a significant effect on psychomotor performance in children with well controlled seizures and low PHT concentrations. However, the results did not preclude the possibility of significant PHT effects when the comparison is between no AED and PHT. Forsythe et al (1991) found minimal cognitive effects (impaired speed of information processing) in children. However, the mean levels of PHT were low and this may limit the generalization of the results, as the doses might have been lower than needed to cause cognitive effects.
Another review (Loring DW et al, 2004) focusing on the cognitive effects of AEDs in childhood concluded that the relative effects of AEDs (apart from phenobarbitone) are largely unknown. They attributed this difficulty to the design of most studies (open label, underpowered, non-randomised, inappropriate controls, and inadequate duration). The SIGN guideline concludes that "the few well controlled studies do not demonstrate significant cognitive impairment with clobazam, sodium valproate, carbamazepine or phenytoin". The SmPC of the brand leader does not specifically mention effects on cognitive function, although effects in the CNS, such are decreased coordination, slurred speech, mental confusion, somnolence, dizziness and drowsiness, are included.
The rapporteur considers that the results from the studies mentioned above are mixed and no definitive conclusions can be drawn. It is difficult to accurately describe or quantify specific effects of phenytoin on cognition based on the available literature. Although significant cognitive impairment has not been proven following phenytoin use, some effects in specific domains of cognition have been found. Even minimal to

moderate effects on cognition might have an important impact in the child's and adolescent's academic and social life. The rapporteur therefore considers that the SmPC should include a sentence about the risk for phenytoin induced cognitive impairment. The following wording is proposed to be included in section 4.8 of the SmPC: "There is some evidence that phenytoin therapy in children may have an impact on cognitive function. However, it is difficult to distinguish the effects of phenytoin on cognition from the effects due to the aetiology of epilepsy, the type and frequency of seizures and concomitant antiepileptic therapy."

Congenital malformations:
PHT is a known teratogen and its effects are described in the SmPC. No new data were identified as part of this procedure.

Gingival overgrowth and potential benefit from folate use:
A common side effect of PHT administration is gingival overgrowth (GO). The pathogenesis of this effect is not entirely understood but appears to be multifactorial. Around 30-50% of patients taking PHT develop significant gingival alterations and it seems to be more prevalent in children. It is not yet determined whether this effect is related to increased levels of circulating drug (Correa JD., 2011). Treatment and prevention of drug-induced GO remains unsatisfactory. For some patients, the change in drug therapy should be considered, a plaque control program might be performed and, in some cases, surgical elimination of the gingival tissue might be needed.

Phenytoin has been associated with folate deficiency. It has also been postulated that there might be a correlation between low levels of folate and phenytoin-induced GO. Arya et al had therefore conducted a prospective placebo controlled study, providing evidence that folic acid decreases the incidence of GO in children on PHT, followed up for 6 months. The rapporteur considers that longer follow up of the patients would have provided more information. It was not determined if folate slows down the development of GO or it has a preventive mode of action. In this study folate levels were not measured and therefore it cannot be determined whether patients had low levels which might have led to the development of GO.
Prasad VN et al (2004) also found that folic acid delays the onset and reduces the incidence and severity of phenytoin-induced GO in children. There is also some evidence that topical folate inhibits phenytoin-induced GO to a greater extent than systemic folic acid (Drew et al, 1987). However, a randomised placebo controlled study in adults (Brown et al, 1991) did not confirm this beneficial effect of folate supplementation.
On the other hand, folic acid supplementation may cause a decrease in serum concentrations of phenytoin, probably by enhancement of PHT metabolism, with the risk of precipitation of seizures (Lewis DP et al, 1995).
The rapporteur did not identify any published recommendations or guidelines for the use of folate for the prevention or treatment of GO.
There is evidence that folate supplementation could offer benefit in children on PHT for the prevention of PIGO. However, there is also evidence that folate can potentially cause a decrease in serum concentrations of phenytoin with the risk of precipitation of seizures. In light of these uncertainties, the rapporteur is of the view that a recommendation for folate supplementation to reduce the incidence of phenytoin induced gingival overgrowth should not be included in the SmPC at this stage. Further long term controlled studies that will examine the effect of folate in PIGO and seizure control are needed before robust recommendations can be made.

Effects on bone mineral density (BMD):
One study examined the effect of three AEDs and phenytoin in bone mineral density (Chung S et al, 1994). It has been long recognised that patients on AEDs are at increased risk of bone loss and fractures. Chung et al. (1994) demonstrated a decrease in total body and lumbar spine BMD in children taking phenytoin more than 2 years. Gissel T. et al (2007) in their review of adverse effects of antiepileptic drugs on bone mineral density in children stated that phenytoin may induce a decrease in lumbar spine and total

body BMD with prolonged use. This was observed in a population probably deficient in vitamin D, whereas similar effects were not observed in two studies excluding children with metabolic bone disease. They therefore concluded that further data are needed to evaluate the effects of phenytoin on BMD.
In 2011 the European Medicines Agency's pharmacovigilance working party (EMA- PhVWP) concluded its class review of antiepileptics and risk of bone disorders, including decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term treatment. As a result of this review, it was recommended to include harmonised information in the SmPCs and package leaflets (PLs) of all medicinal products in the EU containing carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine or sodium valproate. Relevant information is included in the SmPC of phenytoin.

Frequency of gingival overgrowth, hirsutism and hypertrichosis in the paediatric population
From this study but also evident in many studies, it appears that phenytoin induced GO is common in children. The rapporteur did not identify data from large epidemiological studies regarding the prevalence of PIGO. There is wide variation in the literature regarding the prevalence of phenytoin induced gingival hyperplasia in children. Incidence rates from several reports in children range from 13-50% (Thomason JM, Casetta I, Herranz JL, 1988). Even considering the lowest incidence rates reported, this adverse effect is common. Similarly, hirsutism and hypertrichosis are mentioned as common side effects of therapy with PHT in children (Friedman MJ et al, 2006, Herranz JL et al, 1988). However, the SmPC in section 4.8 under the heading "Connective tissue" states: "Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis, Peyronie's Disease and Dupuytren's contracture may occur rarely." It should be noted that section 4.8 of the SmPC of the brand leader does not include a tabulated list of adverse reactions with their respective frequency. These products are old and their SmPCs probably not in line with the "EC Guideline on summary of product characteristics, 2009".
The rapporteur considers that the SmPC should accurately reflect the incidence of these adverse effects in the paediatric population. Although large epidemiological studies regarding the prevalence of gum hyperplasia, hirsutism and hypertrichosis due to long term oral therapy with phenytoin in children could not be found, it appears that they occur commonly.

The MAHs are requested to review their safety data (from clinical trials, post authorisation safety studies and spontaneous reporting) and the published literature and decide whether there are any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and paediatric populations. The MAHs are requested to review these data with regard to the adverse reactions mentioned in the SmPC including the ones identified by the rapporteur (gingival overgrowth, hirsutism and hypertrichosis). If the observed safety profile is different in children compared to adults, the MAHs should propose appropriate wording to update section 4.8 of the SmPC under a separate paediatric heading in order to reflect the incidence and severity of adverse effects in the paediatric population.

MAH3 submitted two publications relating to unlisted adverse effects of phenytoin, i.e. renal tubular dysfunction and choreoathetosis, but concluded that at present these reports do not warrant any regulatory action.

Choreoathetosis:
Dyskinesias are a recognised but unusual side effect of phenytoin. There are many published cases of choreoathetosis in children treated with PHT as presented below:

- Krishnamoorthy, 1983: 3 cases in children less than 2 years, cessation of symptoms after discontinuation of PHT. The events occurred with therapeutic levels.
- Chalhub, 1976: 2 children 8 years old. The events occurred with therapeutic levels.
- Montenegro MA et al (1999) reported 2 children with choreoathetosis.
- Barvaliya M, 2011: 3 years old who developed chorea and recovered after withdrawal of phenytoin.

- Sandyk R: 5 year old child with epilepsy and underlying brain damage developed choreo-athetosis during intoxication with phenytoin. The choreoathetoid movements ceased 4 weeks after discontinuation of the drug.
Phenytoin induced dyskinesias may occur with normal serum phenytoin levels as well as toxic levels and frequently disappear after phenytoin withdrawal.

The SmPC of the brand leader mentions: "There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs." The rapporteur therefore considers that the risk of dyskinesia is adequately reflected in the SmPC. The MAH will continue to monitor cases of choreoathetosis during routine pharmacovigilance activities.

Renal tubular dysfunction:
The renal effects of phenytoin are not well studied and renal dysfunction has not been traditionally associated with phenytoin. Acute tubule-interstitial nephritis has been reported in the context of a generalised hypersensitivity reaction (including DRESS: drug rash with eosinophilia and systemic symptoms) and not mediated by direct toxicity. MAH3 also reported 2 cases were tubulointerstitial nephritis was associated with a hypersensitivity-type reaction. Interstitial nephritis is the only renal undesirable effect mentioned in section 4.8 of the SmPC. The rapporteur could not identify other reports relating to less clinically pronounced (compared to interstitial nephritis) tubular dysfunction in patients receiving phenytoin. The clinical significance of the increased metabolites found in the study by Korinthenberg R et al (1994) is unknown.
The rapporteur considers that the MAH should continue monitoring cases of renal complications and review the data when they become available.

The rapporteur concludes:

- The currently approved SmPC of the brand leader describes the adverse effects of gingival overgrowth, hirsutism and hypertrichosis as rare. However, the rapporteur based on the available literature considers that these side effects are common in children treated with phenytoin. The MAHs are requested to review their safety data and the published literature for any differences in the safety profile of phenytoin between children and adults. If the observed safety profile is different in children compared to adults, the MAHs should propose appropriate wording to update section 4.8 of the SmPC under a separate paediatric heading in order to reflect the incidence and severity of adverse effects in the paediatric population.
- A statement about the risk of cognitive effects of phenytoin in children should be included in section 4.8 of the SmPC: "There is some evidence that phenytoin therapy in children may have an impact on cognitive function. However, it is difficult to distinguish the effects of phenytoin on cognition from the effects due to the aetiology of epilepsy, the type and frequency of seizures and concomitant antiepileptic therapy."

V. RAPPORTEUR'S CONCLUSION AT DAY 70 AND REQUEST OF SUPPLEMENTARY INFORMATION

Phenytoin is an antiepileptic drug (AED) widely used for many decades for the treatment of partial and generalised tonic clonic seizures in children. However, due to its safety profile phenytoin use has been limited in developed countries as second or third line treatment. Its place in the chronic management of epilepsy in children (and adults) differs substantially between developing and developed countries.

The SmPC recommended paediatric doses are commonly used in the literature, as evident from most studies submitted during this procedure and are in line with the BNF for children and the World Health Organisation dosing recommendations. Phenytoin exhibits non-linear pharmacokinetics and a small increase in dose can result in a large change in serum drug levels. Therapeutic drug monitoring of serum drug levels to achieve target therapeutic concentration is therefore important for the safe and effective use of phenytoin in the paediatric population. The dose needs to be adjusted (based on serum levels monitoring) to achieve the optimal clinical outcome for the individual patient.

Phenytoin is additionally indicated for the control of status epilepticus of the tonic-clonic (grand mal) type, for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury, for the treatment of trigeminal neuralgia as second line therapy and for the treatment of cardiac arrhythmias where first line therapy is not effective. The rapporteur considers that the data submitted as part of this work sharing procedure have not provided any new evidence to warrant any changes in these indications.

The rapporteur concludes that no changes are needed in the approved paediatric indications and in the posology for children.

Phenytoin has a known safety profile and its adverse effects are widely described in the literature.
The MAHs reviewed PSUR data and cases of adverse events published in the medical literature and stated that no new safety data that would impact on the products' risk benefit assessment were identified.

The rapporteur reviewed the data submitted by the MAHs as well as other relevant literature reports and concludes that the paediatric use of phenytoin is well established in the management of seizures and overall the drug's benefit:risk has not changed following this procedure.

However, the rapporteur has identified some issues that might warrant updates in the current SmPC of phenytoin:

1. It has been reported in the literature that changing brands of phenytoin resulted in changes in seizure control in adults and children. "Reports of loss of seizure control and/or worsening of side effects around the time of switching between products could be explained as chance associations, but a causal role of switching could not be ruled out in all cases" (CHM, MHRA, 2013).

2. It is noted that the SmPC of phenytoin in section 4.4 states: "Phenytoin is not effective for absence seizures". However, a warning that phenytoin may aggravate this type of seizures does not exist.

3. Although it is difficult to accurately describe or quantify specific effects of phenytoin on cognition based on the available literature, the rapporteur considers that a statement about the risk of cognitive effects of phenytoin in children should be considered.

The MAHs were requested to review their safety data (from clinical trials, post authorisation safety studies and spontaneous reporting) and the published literature and decide whether there are any clinically relevant differences between the safety profile of phenytoin between the adult and paediatric populations. The MAHs were requested to review these data with regard to the adverse reactions mentioned in the SmPC, including the ones identified by the rapporteur (gingival overgrowth, hirsutism and hypertrichosis). If the observed safety profile is different in children compared to adults, the MAHs should propose appropriate wording to update section 4.8 "Undesirable effects" of the SmPC under a separate paediatric heading in order to reflect the incidence and severity of adverse effects in the paediatric population.

VI. COMMENTS FROM MSs AT DAY 85

Following the circulation of the Day 70 PdAR, the rapporteur received comments from FR and SE. FR fully supported the rapporteur's overall conclusion and request for additional information. SE agreed with all but one of the recommendations made by the rapporteur. Specifically, SE stated that they agree with the rapporteur that switching between different phenytoin products should not be recommended. However, SE added that as this is a national decision and therefore it should not be included in the SmPC.

VII. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

1. Comments from MAHs' to rapporteur's proposals for SmPC updates in sections 4.2, 4.4 and 4.8

Comments from MAH3

The MAH concurred with the concern regarding the impact of switching between different phenytoin products on individual patients. The MAH also agreed that a warning about the risk of precipitating or aggravating absence or myoclonic seizures with the use of phenytoin should be included in section 4.4.

To evaluate the potential for cognitive effects of phenytoin in children, the MAH has conducted a search of published literature and a review of relevant cases in the MAH's safety database.
The following databases were searched for articles published through 31 March 2014 that describe cognitive effects in the paediatric population during phenytoin administration:

- MEDLINE 1947-present and MEDLINE In-Process
- BIOSIS Previews 1969 to present
- Derwent Drug File 1964 to present
- EMBASE 1980 to present and EMBASE Daily Alerts

All articles referencing phenytoin and cognitive function were reviewed for any relevant information regarding use in children less than 18 years of age.
55 publications were identified as being relevant to phenytoin and cognitive function in children. Cases of mental retardation, cognitive impairment, and mental changes in children while on phenytoin therapy are described in the literature. However, the MAH considered that the effects of antiepileptic drugs, including phenytoin, on cognition and behaviour were inconclusive based on a review of these articles, and editorial comments from the authors. All antiepileptic drugs were shown to affect certain cognitive abilities; however, the authors maintained that it was difficult to separate the effect of the underlying antiepileptic therapy from physiological effects known to be associated with epilepsy. Once anticonvulsant therapy was started, it was not possible to determine whether cognitive changes were due to the anticonvulsant or to pre-existing factors, since baseline testing was not carried out prior to the commencement of anticonvulsant therapy.

A large variation in cognitive function exists within each type of epilepsy. Epilepsy can occur following brain damage, can be linked to congenital CNS anomalies, or could be attributed to other CNS disorders.

Any of these factors could contribute to cognitive impairment, with or without anticonvulsant therapy. In addition, seizure type, age of onset and number of seizures may also impact on cognitive impairment.

Forsythe et al (1991) reported on a study in which 64 new cases of childhood epilepsy were randomly assigned to carbamazepine, phenytoin, or sodium valproate, and were assessed with cognitive tests before medication and 3 subsequent times over a year. The authors reported that carbamazepine in moderate dosage adversely affected memory, but sodium valproate and phenytoin did not.
Devinsky et al. (1995) reported that most of the major anti-epileptic drugs (AEDs), administered in therapeutic doses, cause little or no cognitive or behavioural impairment. In addition, the authors reported that the results from several well-controlled studies did not demonstrate significant differences between the effects of phenytoin and those of carbamazepine or valproate. In addition, Drane et al. (1996) reported that the cognitive effects of major AEDs, including phenytoin, carbamazepine, and valproate, appeared modest when dosages were kept within the standard therapeutic ranges and polypharmacy was avoided.
Williams et al. (1998) studied 37 children over a 6-month period. The authors concluded that there were no significant differences in cognitive or behavioural scores after 6 months of anticonvulsant treatment when comparing the epileptic and control children.

MAH's safety database was also searched for all phenytoin reports that were received through 31 March 2014 that reported a primary MedDRA PT under the MedDRA High Level Group Term (HLGT) Cognitive and attention disorders and disturbances or the HLGT Mental impairment disorders. Terms under the HLT Dementia and under the HLT Alzheimer's disease were excluded.
The MAH provided the following summary of findings: the cognitive-related events described various neuropsychiatric symptoms. There was variability in the percentage of events reported in the paediatric versus non-paediatric groups with low frequencies of events in both groups. Overall, there were a higher percentage of events reported in the non-paediatric group.
The cases in the paediatric group demonstrate that the duration of use of phenytoin ranged from a limited neonatal exposure after birth to 2 years. 11 of the 29 paediatric reports provided limited information, thus precluding any meaningful assessment. Many cases provided alternative explanations (such as fetal distress and anoxia at delivery, hypoglycaemia, psychiatric illness, brain injury, history of autism, history of attention deficit disorder, and genetic disorders) for cognitive development effects. All except 4 reports provided suspect or concomitant medications for comorbid conditions, with many cases reporting multiple AEDs, and numerous changes in therapy regimes.
The most frequently reported cognitive-related event in the paediatric group was Disturbance in attention (n=8). Verbatim events included "decreased level of concentration" 3 days after an 11-year-old autistic male started phenytoin, "impaired concentration" in a patient who recovered from a coma; "difficulty concentrating" in a patient who recovered from severe drug reaction with eosinophilia and systemic symptoms (DRESS); "difficulty concentrating in school" in a patient who also experienced extreme fatigue; "lack of concentration" after switching to a different brand of phenytoin in a patient who had a history of an unspecified genetic disease, which caused hyperactivity, mental delay and epilepsy; and "not being able to think straight" since starting phenytoin.
There were 8 reports of mental retardation in the paediatric group. One report described a child with retardation and numerous physical and mental defects who was born to a mother who received phenytoin and is, therefore, not relevant to this discussion. In the remaining 7 reports, insufficient information was provided regarding the onset of the retardation, as it was noted among conditions describing the patient's status at presentation.

MAH's conclusion for Review of Cognitive Effects in Children:
The literature on the effects of antiepileptic drugs on cognition and behaviour is inconclusive. All antiepileptic drugs have been shown to affect certain cognitive abilities; however, it remains difficult to separate the effect of the drugs from the known cognitive effects potentially associated with epilepsy. A review of the safety database showed that for most events, there were a higher percentage of events reported in the non-paediatric group. The numbers of events and associated reporting proportions do not

provide evidence of disproportionate risk of the occurrence of cognitive effects in the paediatric patient population.
As a result of a review of the literature relevant to phenytoin and cognitive function as well as the MAH's safety database, the MAH concluded that there is not enough evidence to support an association between phenytoin use and adverse effects on cognitive function in children. Therefore, the MAH considers that no change to Section 4.8 of the SmPC regarding a risk of cognitive effects of phenytoin in children is warranted at this time.

Comments from MAH4
The MAH has agreed with all the rapporteur's recommendations to update the SmPC of Phenytoin.

Comments:

Only one MAH (MAH3) provided data discussing whether the inclusion of a sentence on the risk of adverse neurocognitive effects of phenytoin in children is appropriate. MAH3 based on a literature search and the MAH's safety database concluded that there is not enough evidence to support it.
The rapporteur review of the provided data is as follows:
The studies by Forsythe I et al (1991) and Aman et al, were described in previous sections as well as the conclusions drawn by various authors that reviewed the cognitive effects of AEDs in children and adults. The study by Aldenkamp A.P et al. (1993) was also previously discussed; children on PHT had slower speed of information processing than children on CBZ, however, this statistically significant finding was observed only in 1 of 12 tests which could potentially be a chance finding. The number of patients on PHT (N=10) is also very low to make any valid comparisons.
MAH3 briefly mentioned another study by Williams et al (1998). This study did not find cognitive adverse effects from AED monotherapy during the first 6 months compared to a control group. However, only one patient was treated with PHT.

Finally another study by Andrews et al (1984) was identified by the rapporteur. This was a study of new referrals (adolescents and adults) with epilepsy recently started on treatment with either carbamazepine or phenytoin, in which the groups of patients compared were of similar age, IQ and seizure type, suggested that phenytoin can adversely affect memory and performance on a tracking task. The patients had well controlled seizures. Randomisation is not mentioned in the paper. There are also no tests performed at baseline, before the initiation of treatment and therefore not known whether the differences observed can be attributed to treatment effect or to differences in baseline characteristics.

There are also a number of studies examining the cognitive effects of PHT in healthy volunteers and adults with epilepsy. However, the relevance of their results to the paediatric population is not certain.

The rapporteur concludes that cognitive performance in children with epilepsy is affected by many factors which can be interrelated. These are: the underlying brain pathology, type of epilepsy and seizures, seizure severity and frequency, subclinical epileptiform activity, level of control of seizures with therapy, age of onset, treatment duration, choice or combination of antiepileptic drugs, psychosocial problems. Therefore any study attempting to investigate the relative contribution of one of these factors on cognition is very difficult.
Although PHT is widely used in children, very few studies examining its cognitive effect in children. The few available studies have several methodological limitations such as small sample size, absence of control (with healthy individuals or no treatment group or placebo group), absence of randomisation, lack of baseline assessments. Keeping in mind these limitations, it is noted that negative effects on cognition are not reported in all studies.
It is therefore concluded that as the available literature does not offer conclusive evidence on the effects of PHT in cognition, a warning should not be added in the SmPC.

2. MAHs' responses to request for supplementary information on the safety profile of PHT in children

MAH1:
The MAH searched their database and the recent literature and stated that they have not identified any clinically relevant differences between the adult and paediatric populations with regards to the safety profile of phenytoin.

MAH3:
To evaluate clinically relevant differences in the safety profile of phenytoin between the adult and paediatric populations, the MAH has conducted a review of published literature and a review of the safety database.

Literature data
To supplement the literature review provided in the initial Article 45 response, the following published literature databases were searched for articles to include the period 01 January 2013 to 31 March 2014, describing the use of phenytoin in children:

- MEDLINE 1947-present & MEDLINE In-Process
- BIOSIS Previews 1969 to present
- Derwent Drug File 1964 to present
- EMBASE 1980 to present and EMBASE Daily Alerts

7 articles were identified:
- A case report (Ali Ekici M et al, 2013) of phenytoin-induced stuttering in a 3-year-old boy 10 days after an infusion of 20 mg/kg phenytoin and then maintenance dose 5 mg/kg/day. Magnetic Resonance imaging (MRI) showed no abnormalities and phenytoin concentration in serum was 0.85 mg/mL at the time of phenytoin cessation. The authors reported this as a first case of phenytoin-induced stuttering with an unknown mechanism.
- A case report (Chhabra P et al, 2013) that described compartment syndrome, a rare complication of purple glove syndrome, in a 16-year-old male, after injection bolus of phenytoin 1000 mg in normal saline. The patient was a non-smoker with no history of diabetes. The patient had a history of Tetralogy of Fallot.
- An article (Gaeti WP et al, 2013) described 2 cases of DRESS associated with phenytoin.
- Another 2 articles (Husain Z et al, 2013 and Lo MH et al, 2013) provided additional references concerning DRESS in children treated with phenytoin.
- A case report (Kumar N et al, 2013) describing phenytoin-induced cerebellar atrophy (MRI confirmed) in a 16-year-old male with a viral infection. The patient had been receiving oral phenytoin 5 mg/kg once daily for 10 years. In addition, he had a high phenytoin concentration of 30 µg/mL. After withdrawing phenytoin and receiving valproic acid, the patient was reported as recovering.
- A case report (Mondal R et al, 2013) of phenytoin-induced, life-threatening macroglossia in an 8-year-old boy without diagnosis of DRESS syndrome or pseudolymphoma. There was no history of headache or vomiting, respiratory distress, swelling of face, itching, and loose stool. In addition, there was no family history of atopy or similar type of episodes. The patient was recovering with treatment. The authors report this association as a first case, not previously described.

As a result of a review of these 7 articles, the MAH concluded that no new safety signals were identified concerning phenytoin use in paediatrics.

MAH's safety database
To identify possible differences in the AE reports between children and adult phenytoin users, events in paediatric patients were reviewed and compared with events in non-paediatric patients, and relative reporting rate ratios were calculated. Events whereby the relative reporting rate ratio was greater than or equal to 3 and when there were at least 3 events reported for the paediatric population were further assessed. The data was updated through 31 March 2014.

Reporting percentages by MedDRA SOC showed that, other than the Congenital, familial and genetic disorders SOC, there were no data that indicated any particular areas that were reported with a substantially higher frequency in the paediatric group. Skin and subcutaneous tissue disorder events showed the greatest difference between the 2 groups, as they were reported more frequently in the paediatric population (38.4%) compared with the non-paediatric population (28.5%). More frequently reported DRESS, Stevens Johnson syndrome, and a variety of rashes in the paediatric group, account for the higher reporting proportion.
Using the same methodology, AEs reported to the MAH's database (up to march 2014) were reviewed. Events new (compared to the previously submitted data by the same MAH during this procedure) in demonstrating a reporting rate ratio of ≥3 and that were reported at least 3 times in the paediatric population are presented below:

Brain Stem Syndrome
Of the 3 cases of Brain stem syndrome in the paediatric group, 2 reports were from the same literature article that described events in 2 children with phenytoin toxicity. Both children exhibited brain-stem and cerebellar symptoms. The events resolved when therapy was discontinued. In the remaining case, the patient experienced an "immature brain," which was attributed to use of hexachlorophene.
MAH's conclusion: On the basis of the review of these cases, no new safety issue for the paediatric population was identified, as the term captured non-specific findings.

Choreoathetosis
Review of the 9 paediatric reports of choreoathetosis revealed that the event was temporally related to phenytoin administration. These children ranged in age from 44 months to 16 years. All reports originated from published literature. In 6 cases (66.7%), high phenytoin levels or phenytoin intoxication were reported. The drug level in 2 cases was not reported; in the remaining case, the patient's phenytoin level was within normal limits and it was uncertain if choreoathetosis was noted before phenytoin therapy was initiated. Of the 9 cases, 7 positive dechallenges were reported.
The Phenytoin SmPC lists dose-related central nervous system (CNS) effects as a common manifestation encountered with phenytoin therapy. It states that there have been rare reports of Dyskinesias, including chorea, dystonia, tremor, motor twitching, and asterixis. While this event was reported in the safety database more frequently in the paediatric group (0.7%; 9 event in 1350 cases) compared with the non-paediatric group (0.2%; 23 events in 11,813 cases) driven by the cases highlighted in the literature, no conclusions regarding a true additional risk in children can be drawn.

Crying
The 6 paediatric reports of crying were reviewed. 5 of the patients were 4 years of age or younger. The reports described crying with falling, pain, crankiness, and sadness, but provided limited information for meaningful analysis. One report described a 7-week old male who on the fourth day of therapy became fretful, frantic, and cried "a lot" 15 minutes after receiving 1 mL phenytoin paediatric suspension. Phenytoin was discontinued and the symptoms resolved. In the remaining case, an 11-year-old male was crying and anxious when having palpitations after phenytoin was discontinued.
MAH's conclusion: On the basis of the review of these cases, no new safety issue for the paediatric population was identified.

Altered State of Consciousness
The 3 paediatric reports of altered state of consciousness were reviewed. In all 3 cases, the events were associated with elevated phenytoin levels.
MAH's conclusion: On the basis of the review of these cases, no new safety issue for the paediatric population was identified.

Hypotonia
There were 5 reports of hypotonia in the paediatric group. All reports described children who experienced hypotonia (floppiness, generalized flaccidity, hypotonic muscles) in addition to other neurologic

symptoms. All children were found to have high phenytoin levels and the hypotonia recovered or improved with phenytoin discontinuation or dose reduction.

Urinary Retention
There were 3 reports of urinary retention in the paediatric group. Two reports provided minimal information. One report from published literature described urinary retention that developed several hours after intravenous phenytoin administration in an 8-year-old female with severe cerebral palsy, microencephaly, and retardation. She required intermittent bladder catherisation while receiving phenytoin to control seizures. After phenytoin therapy was stopped, the urinary retention resolved. Following another seizure, phenytoin was restarted and within 8 hours, she experienced urinary retention again. The event resolved when phenytoin was discontinued.
MAH's conclusion: On the basis of the review of these cases, no new safety issue for the paediatric population was identified.

Urine Copper Increased
All reports of PT urine copper increased originated from a single 1966 literature article titled Abnormal copper and tryptophan metabolism and chelation therapy in anticonvulsant drug intolerance. The article described a study of 41 patients who were receiving anticonvulsant medications, including 28 patients who were receiving diphenylhydantoin. Some of them also received phenobarbital or primidone (Mysoline) in combination with diphenylhydantoin. The urinary excretion of copper, zinc, and lead were quantitatively determined at random and/or 24-hour samples. These 14 reports captured phenytoin patients in the study (10 adults and 4 paediatric) who had elevated urine copper levels. Seven patients were chelated with dimercaptopropanol and/or disodium calcium ethylenediaminetetraacetic acid (EDTA), after which there appeared to be clinical improvement in 6 of the 7 patients.
The cases from a single literature study are the only reports of Urine copper increased, which occurred in 14 of the 28 patients who were receiving phenytoin (4 paediatric cases and 10 non-paediatric cases).
MAH's conclusion: On the basis of the review of these cases, no new safety issue for the paediatric population was identified.

Finally, MAH3 performed a search through 31 March 2014 to identify cases were the outcome was death. Among the 1350 cases in the paediatric group identified, there were 67 reports (5.0%) with at least 1 fatal event in infants, children, or adolescents who received phenytoin. The proportion of death reports in the paediatric cases (5.0%) was comparable to the frequency of death reports in the non-paediatric cases (5.2%).
Long-term studies have demonstrated an increased mortality risk among children with epilepsy compared with the general population. The causes of death reported in paediatric phenytoin patients did not identify a safety concern in this patient population. The events occurring most frequently are adequately described in the CDS and SmPC.
MAH's conclusion: On the basis of this review, no changes to product labelling are warranted regarding fatal events in children.

MAH3 discussion on adverse events identified by the rapporteur as potentially being more frequent in the paediatric population:

- Gingival overgrowth
Risk factors for gingival overgrowth in phenytoin patients include presence of gingival inflammation resulting from poor oral hygiene and susceptibility of some subpopulations of fibroblasts and keratinocytes to interaction with phenytoin. Some studies found that younger age is a risk; however, the subjects in some studies were hospitalized or institutionalized children, or were a relatively young population that did not reflect the normal age range of phenytoin users.
Small studies, with variations in phenytoin dosages, length of exposure and differences in ages included in the studies, reported a wide range of incidences of phenytoin-induced gingival overgrowth from 3% to

57%. The incidence of gingival overgrowth in the normal population was reported to range from 4% to 7.5% (Nayyar AS et al, 2012).
The MAH identified 44 publications as being relevant to phenytoin and gingival overgrowth in children less than 18 years of age. The MAH concluded that the association of phenytoin administration in children and gingival overgrowth is well documented in the literature. This association is more prevalent in the paediatric population when compared to adults and this may be reflective of less robust dental hygiene in the children studied.
The MAH's safety database was searched for all phenytoin reports that were received through 31 March 2014 that reported any of the following MedDRA (Version 16.1) PTs that were indicative of gingival overgrowth: Gingival hyperplasia, Gingival hypertrophy, Gingival disorder, Gingival swelling. Absolute counts were relatively low for the PTs of interest in the paediatric group; however, the proportional reporting rate for the PT Gingival hyperplasia was higher in the paediatric group (2.0%) compared with the non-paediatric group (0.9%). Likewise, for Gingival hypertrophy, the reporting rate was higher for the paediatric group (0.5%) compared with the non-paediatric group (0.2%). The reporting rates for the PTs of Gingival swelling and Gingival disorder were lower in the paediatric group.
On the basis of this review, the MAH proposed to add information that this event occurs more frequently in paediatric patients and in patients with poor oral hygiene.

- Hirsutism
8 publications were identified in the literature as being relevant to phenytoin and hirsutism in children less than 18 years of age. Articles published through 31 March 2014 were searched for the PTs Hirsutism, Hyperhydrosis, and Hair growth abnormal in the paediatric population. Hirsutism in patients administered phenytoin is described in the literature. However, the event is not described to occur more frequently in the paediatric population when compared to the non-paediatric population.
The safety database was searched for all phenytoin reports received through 31 March 2014 that reported the MedDRA (Version 16.1) PT Hirsutism. While the proportional reporting rate for the PT Hirsutism was higher in the paediatric group (0.6%) compared with the non-paediatric group (0.1%), the overall number of reports in the cumulative paediatric and adult dataset is low (8 and 15, respectively).
On the basis of this review, the MAH concluded that no substantial differences concerning phenytoin use and hirsutism in the paediatric versus the adult population were identified.

- Hypertrichosis
Hypertrichosis is a condition which refers to diffusely increased total body hair growth. This is a rare condition that may be caused by a drug, examples of which include phenytoin, penicillamine, diazoxide, minoxidil, and cyclosporine. Hypertrichosis can also occur in patients with some systemic illnesses such as hypothyroidism, anorexia nervosa, malnutrition, porphyria, and dermatomyositis, and as a paraneoplastic syndrome in some patients.
Hypertrichosis in paediatric patients administered phenytoin is not well described in the literature, since only one relevant article (Livingston S et al, 1980) was retrieved after a cumulative search.
The safety database was searched for all phenytoin reports received through 31 March 2014 that reported the MedDRA (Version 16.1) PT Hypertrichosis. There were 6 reports of the PT Hypertrichosis in the paediatric group. In addition to the PTs of Hirsutism and Hypertrichosis, the safety database was also searched for all phenytoin reports received through 31 March 2014 that reported the MedDRA (Version 16.1) PT Hair Growth Abnormal. Overall, the reports of Hair growth abnormal provided limited information. No significant trends or differences between the paediatric and non-paediatric groups were noted.
On the basis of this review, the MAH did not identify any additional safety issues concerning phenytoin use and hypertrichosis in the paediatric population and therefore concluded that no changes to the SmPC are warranted.

MAH4
The MAH has performed an internal review of all safety data entered in its Global Safety Database (MedDRA versions 13.1-16.1), including literature cases. Recordati confirmed that no cases of gingival

overgrowth, hirsutism and hypertrichosis were entered in its Global Safety Database, neither in paediatric nor in adult population. Additionally, a new literature search identified no new safety signals regarding the paediatric use.

Comments:

MAH3 provided detailed literature data and cases identified in their safety database examining phenytoin adverse events in children and comparing their relative frequency to that in adults.
No new safety concerns were identified. Some of the identified AEs are already mentioned in the SmPC of PHT, such as choreoathetosis. In addition, brain stem and cerebellar syndrome and altered state of consciousness were all observed with elevated PHT levels. Symptoms/signs relevant to these AEs are mentioned in section 4.9 overdose of PHT SmPC: "The initial symptoms are nystagmus, ataxia and dysarthria. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs followed by respiratory depression and apnoea" and section 4.8 undesirable effects "There are occasional reports of irreversible cerebellar dysfunction associated with severe phenytoin overdosage."
Other AEs identified by the MAH are not mentioned in the SmPC but the rapporteur agrees that based on the available information, there does not appear to be a significant new safety concern.

MAH3 did not identify clinically relevant differences between the safety profile of PHT in paediatric patients compared with adult patients, with the exception of gingival overgrowth.
MAH3 proposed to add SmPC information that the adverse reaction of gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene. The rapporteur agrees with this proposal.
The rapporteur concludes that all SmPCs of phenytoin products should be updated to include the following statement in section 4.8 under the heading "paediatric population":

"The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene."

VIII. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Phenytoin is a widely used antiepileptic drug (AED) in both adults and children. It is indicated for the treatment of partial and generalised tonic clonic seizures in children and adults.

Phenytoin is additionally indicated for the control of status epilepticus of the tonic-clonic (grand mal) type, for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury, for the treatment of trigeminal neuralgia as second line therapy and for the treatment of cardiac arrhythmias where first line therapy is not effective.
Based on the data submitted as part of this work sharing procedure under Article 45, the rapporteur concludes that no changes are needed in the approved paediatric indications and in the posology for children.

Phenytoin has a known safety profile and its adverse effects are widely described in the literature.
The MAHs reviewed PSUR data and cases of adverse events published in the medical literature.
The rapporteur reviewed the data submitted by the MAHs as well as other relevant literature reports and concludes that the paediatric use of phenytoin is well established in the management of seizures and overall the drug's benefit:risk has not changed following this procedure.

The rapporteur has identified issues that warrant updates in the current SmPC of phenytoin:

1. Section 4.4 Special warnings and precautions for use: “PHT may precipitate or aggravate absence seizures and myoclonic seizures”.

2. Section 4.8 Undesirable effects (under a separate paediatric heading): The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

During this work-sharing procedure the rapporteur considered whether a statement in section 4.2 that switching between different phenytoin products is not recommended should be added. This was based on a CHM review indicating that there is a risk of loss of seizure control and/or worsening of side effects when switching from one phenytoin product to another. One member state (SE) stated that they agree with the rapporteur that switching between different phenytoin products should not be recommended but added that this is a national decision and therefore it should not be included in the SmPC.
The rapporteur considers that there is adequate evidence from the literature to support this potential risk of loss of seizure control and/or worsening of side effects in adults and children. However, the rapporteur agrees with SE that both the categorization of phenytoin in category 1 (i.e. at highest risk amongst other antiepileptic drugs), and the advice that patients should be maintained on a specific manufacturer’s product, is a national (UK) decision and cannot be recommended as part of the review of the data in this work-sharing procedure under Article 45.

Finally, following the MAHs’ responses and a comprehensive literature review, the rapporteur concludes that the evidence on adverse cognitive effects of PHT in children is inconclusive and therefore a statement regarding potential cognitive effects should not be added to the SmPC.

SmPC CHANGES

Section 4.4 Special warnings and precautions for use

PHT may precipitate or aggravate absence seizures and myoclonic seizures.

Section 4.8 Undesirable effects

Paediatric population

The adverse event profile of phenytoin is generally similar between children and adults. Gingival hyperplasia occurs more frequently in paediatric patients and in patients with poor oral hygiene.

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X. List of Medicinal products and marketing authorisation holders involved

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form
G.L. Pharma GmbH	AT	Epilan-D 100 mg - Tabletten	100 mg	tablet
G.L. Pharma GmbH	AT	Epilan-D 50 mg/ml-Ampullen	50 mg/ml	solution for injection
G.L. Pharma GmbH	BG	Epilan-D 100 mg tablets	100 mg	tablet
G.L. Pharma GmbH	BG	Epilan D 50 mg/ml solution for injection	50mg/ml	solution for injection
G.L. Pharma GmbH	CZ	Epilan-D-Gerot tablets	100 mg	tablet
G.L. Pharma GmbH	SK	Epilan-D-Gerot tablets	100 mg	tablet
Recordati S.p.A, Milan	IT	Dintoina	100 mg	tablet
NEVADAPHARMA AB	SE	Lehydan	25 mg, 100 mg	Tablet
PFIZER	AT	Epanutin "PFIZER"	30 mg/5ml	Suspension, Oral