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

Valproic acid

Epilim, Epilim Chrono, Epilim Chronosphere, Orfiril, Depamag, Dipromal

UK/W/066/pdWS/001

Rapporteur:	The Netherlands (formerly the United Kingdom)
Finalisation procedure (day 90):	10 April 2020
Date of finalisation of PAR	25 June 2020

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Epilim, Epilim Chrono, Epilim Chronosphere, Orfiril, Depamag, Dipromal
INN (or common name) of the active substance(s):	valproic acid, sodium valproate, magnesium valproate, valproate semisodium (divalproex sodium)
MAH:	Sanofi-Aventis Desitin Arzneimittel GMBH Sigma-Tau (Depamag withdrawn from market) ICN Polfa Rzeszow S.A. (now PharmaSwiss Ceska Republika s.r.o.)
Currently approved Indication(s)	Valproic acid is a broad-spectrum antiepileptic that is widely used in children and adults. - Sodium valproate tablets, oral suspension, and capsules are indicated for the treatment of generalised, partial or other epilepsy in adults and children 0-18 years of age. - Valproate as valproate semisodium (or Divalproex sodium) is indicated to treat manic episodes in bipolar disorder in adult patients when lithium is not tolerated or is contraindicated. - Sodium valproate as a parenteral solution is indicated for the treatment of epileptic patients who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated
Pharmaco-therapeutic group (ATC Code):	N03AB02
Pharmaceutical form(s) and strength(s):	100mg crushable tablets, gastro-resistant tablets (200mg, 500mg), controlled-release tablets (200mg, 300mg, 500mg) , prolonged release granules (100mg, 250mg, 750mg, 1000mg), modified release granules (50mg, 100mg, 250mg, 500mg, 750mg, 1000mg), syrup 200mg/5ml, injection solution (300mg/3ml)

LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
AE	Adverse Events
AEDs	Antiepileptic Drugs
BD	Bipolar Disorder
CCSI	Company Core Safety Information
CNS	Central Nervous System
IV	Intravenous
MAH	Marketing Authorisation Holder
NOAEL	No-Observed-Adverse-Effect Level
PK	Pharmacokinetics
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RCT	Randomised Control Trial
SD	Sprague-Dawley
SE	Status Epilepticus
SmPC	Summary of Product Characteristics
SOC	System Organ Class
VPA	Valproate

I. EXECUTIVE SUMMARY

On the basis of data submitted by the marketing authorisation holders (MAHs) as well as other relevant literature reports changes in the summary of product characteristics (SmPC) sections 4.8 and 5.2 and package leaflet (PL) section 4 are necessary.

Summary of outcome

☐ No change

☒ Change

- ☒ New study data: section 5.2
- ☒ New safety information: SmPC section 4.8 and PL section 4
- ☐ Paediatric information clarified
- ☐ New indication

II. RECOMMENDATION

Changes are recommended to SmPC section 4.8 and 5.2 and PL section 4:

For products licensed for paediatric use:

SmPC, section 4.8

Paediatric population

"The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population."

SmPC, section 5.2

"Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults."

PL, section 4

"Additional side effects in children

Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, infection of the pancreas (pancreatitis), aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder."

For products not licensed for paediatric use:

SmPC, section 4.8

Paediatric population

"The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric

disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population."

PL, section 4
"Additional side effects in children
Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, infection of the pancreas (pancreatitis), aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder."

If appropriate, the following paragraph in section 4.2 should be amended as follows:
Paediatric population
"The efficacy ~~**and safety**~~ of [Product name] in children below 18 years of age <in the treatment of manic episodes of bipolar disorder> has not been established. **With respect to safety information in children see section 4.8.**"

III. INTRODUCTION

Valproic acid is a broad-spectrum antiepileptic. The term VPA will be used in this document for any of the following: valproic acid, its salts (sodium or magnesium valproate) and the mixture of sodium valproate and valproic acid (valproate semisodium). VPA is available in various formulations, i.e. tablet, suspension, capsule, and parenteral solution.

Valproate and related substances are licensed since 1967 to treat epilepsy and since 1995 to treat bipolar disorders in Europe.
Four MAHs submitted completed paediatric studies for valproic acid, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. The MAHs are:

- MAH1: Sanofi-Aventis
- MAH2: Desitin Arzneimittel GMBH
- MAH3: Sigma-Tau
- MAH4: ICN Polfa Rzeszow S.A.

The MAHs stated that the submitted paediatric studies do not influence the benefit/risk ratio for valproic acid and that there is no consequential regulatory action required.
The following documentation has been included as per the procedural guidance:

- All data, including published information, non-clinical and clinically relevant for the paediatric assessment
- A critical expert overview clarifying the context of the data
- 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.

IV. SCIENTIFIC DISCUSSION

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

No information was submitted regarding the formulation used in the paediatric clinical studies

IV.2 Non-clinical aspects

IV.2.1 introduction

MAH1 (Sanofi-Aventis) submitted two unpublished non-clinical studies:

- Study TA91-003: a 4-week intravenous toxicity study in immature rats

- Study TA91-004: a 14-day intraperitoneal toxicity study of sodium valproate injectable in neonatal rats

In addition, the MAH performed a literature review of published-non clinical studies that were mainly focussed on two topics: hepatotoxicity and effect on brain development. Four studies were identified as non-clinical safety information related to juvenile animals.
Furthermore, the MAH provided the tabulated summaries from Sanofi a report, dated 6 September 1999, which provide additional information on repeat dose toxicity studies and segment I fertility studies on effects on testis and fertility in adult rat.

IV.2.2 Non-clinical studies

IV.2.2.1 Study TA91-003

Sodium valproate was administered to 10 male and 10 female Crl:CD®BR immature rats per group by intravenous injection at dosages of 0, 30, 90 or 240 mg/kg/day for 28 consecutive days. Pups were 14 days old at the start of treatment. One male and one female rat that received 240 mg/kg/day died on Day 7. The deaths were considered to be drug-related.
Slightly decreased activity and ataxia were noted in rats given 30 or 90 mg/kg/day. The central nervous system (CNS) effects in these two groups were mild and transient.
The dosage of 240 mg/kg/day produced severe toxic effects including CNS effects (moderate to severe ataxia, loss of righting reflex, decreased activity), decreased body-weight gain, reductions in white blood cells and lymphocyte counts, decreased organ weights of brain (females) and gonads (males), and histopathologic changes in the kidneys of female rats (increased incidence of slight to mild mineralisation at the corticomedullary junction and/or tubular basophilia).
In the two high-dose rats that died on Day 7, histological changes were observed in bone marrow (decreased cellularity), liver (decreased extramedullary haematopoiesis), lymph nodes (lymphocyte depletion), thymus (lymphoid atrophy) and spleen (white pulp atrophy and decreased extramedullary haematopoiesis).
These lesions were not present in any rat necropsied at the end of the 4-week treatment period.
The MAH concluded that daily intravenous injection of sodium valproate in immature rats for 28 days produced severe toxic effects at 240 mg/kg/day. The 90 mg/kg/day dosage was considered as a non-toxic effect level.

IV.2.2.2 Study TA91-004

Sodium valproate (VPA) injectable was administered to 10 male and 10 female Crl:CD®BR Sprague Dawley neonatal rats per group by intraperitoneal injection at dosages of 0, 30, 90 or 240 mg/kg/day for 14 consecutive days. Pups were 4 days old at the start of treatment. The intraperitoneal route was used because the intravenous route was impractical for multiple treatments in the neonatal rat. No drug-related deaths occurred during the study. Intraperitoneal administration of sodium valproate at a dosage of 30 mg/kg/day for 14 days produced no toxicity. A dosage of 90 mg/kg/day produced slightly decreased activity and decreased body-weight gain. A dosage of 240 mg/kg/day produced severe toxic effects that included:

- CNS effects: ataxia, decreased activity, loss of righting reflex;
- decreased body-weight gain (secondary effects caused by reduced activity);
- reductions in white blood cell and lymphocyte counts;
- decreased alkaline phosphatase and glucose;
- increased blood urea nitrogen and bilirubin;
- reductions in absolute and relative organ weights of spleen, brain, thymus, adrenal and testes;
- histopathological changes in bone marrow (decreased cellularity), liver (decreased extramedullary haematopoiesis), lymph nodes (lymphocyte depletion), thymus (lymphoid atrophy), spleen (white pulp atrophy and decreased extramedullary haematopoiesis), kidneys (dilated medullary tubules, tubular mineralisation and increased incidence and severity of cystitis) and eyes (increased incidence of retinal folds/rosettes).

The change in the eyes was considered minimal since it was not associated with inflammation, other intra-ocular abnormalities, abnormal differentiation or disorganization of the retinal layers and, all retinal layers were found in the retinal fold/rosette. In conclusion, the 14-day daily intraperitoneal injection of sodium

valproate in neonatal rats produced severe toxic effects at 240 mg/kg/day. The MAH considered the non-toxic effect dosage level in neonatal rats to be 90 mg/kg/day.

IV.2.2.3 Published non-clinical studies

The MAH performed a literature review in Embase and Medline databases using the following strategy: ['valproic acid'/exp AND [animals]/lim] AND [juvenile OR newborn OR neonate OR neonatal OR young OR immature OR prepuber* OR pup OR puppy OR kitten OR piglet OR infant OR postnatal NOT young:au], and limited to adverse drug reaction or drug toxicity.
The following articles were identified as nonclinical safety information related to juvenile animals. They are mainly focused on two topics, hepatotoxicity and effect on brain development.

General toxicity
Espandiari P, Zhang J, Schnackenberg LK, Miller TJ, Knapton A, Herman EH, et al. Age related differences in susceptibility to toxic effects of valproic acid in rats. J Appl Toxicol. 2008;28(5):628–37.

The objective of this article was to validate an animal model to evaluate drug safety in the paediatric population as suggested in the American Food and Drug Administration guidance for industry "on nonclinical safety evaluation of paediatric drugs" published in February 2006. A multi-age rat model was evaluated as a means to identify a potential age-related difference in toxicity using VPA as a known paediatric hepatotoxic agent.
Different age groups of Sprague-Dawley (SD) rats (10-, 25-, 40-, 80-day-old) were administered VPA at doses of 160, 320, 500 or 650 mg/kg (IP) for 4 days. Animals from all age groups developed toxicity after treatment with VPA; however, the patterns of toxicity were dissimilar within each age group. The high dose of VPA caused significant lethality in 10- and 25-day-old rats. All doses of VPA caused decrease in the platelet counts (10-, 25-day-old rats) and the rate of growth (40-day-old rats) and increases in the urine creatine concentration (high dose, 80-day-old rats). VPA induced hepatic and splenic alterations in all age groups. The most severe lesions were found mostly in 10- and 80-day-old rats. Significant changes in blood urea nitrogen, alanine aminotransferase and alkaline phosphatase were observed in 10-day-old pups after treatment with low doses of VPA. The highest VPA dose caused significant decreases in the levels of serum total protein (40- and 80-day-old rats). Principal component analysis of spectra derived from terminal urine samples of all age groups showed that each age group clusters separately. No significant changes were found in other organs (heart, lung and kidney).
In conclusion, the present study examined the spectrum of VPA-induced toxicity in a multi-age rodent model. Findings indicated that the pattern of toxicity induced by VPA in the different aged SD rats was quite dissimilar; each age group was different from the 80-day-old adults as well as from each other. In this study, the 10-day-old pups were the most sensitive age group to the toxic effects of VPA, a finding which seems to correlate with clinical reports indicating that infants younger than 2 years treated with the drug experience a high incidence of adverse effects related to difference in metabolism.
The MAH concluded that these nonclinical data do not bring new safety information for paediatrics.

Hepatoxicity
Fisher RL, Sanuik JT, Nau H, Gandolfi AJ, Brendel K. Comparative toxicity of valproic acid and its metabolites in liver slices from adult rats, weanling rats and humans. Toxicol In Vitro. 1994;8(3):371-9.

The objective of this article was to investigate the mechanism of VPA hepatotoxicity and determine if this toxicity may be a combination of the formation and action of toxic metabolites in developing tissues.
The authors investigated the action of VPA and its metabolites in liver slices prepared from adult and weanling Sprague-Dawley rats and from human livers (non-transplantable livers from organ donors, or biopsy material from patients undergoing surgical liver resection). VPA, 2-propyl-2-pentenoic acid (2-en-VPA or Δ2-VPA), 2-propyl-4-pentenoic acid (4-en-VPA or Δ4-VPA) were incubated for various times at concentrations of 100 or 300 micrograms/ml.
Protein synthesis and K+ content were used to assess functional integrity or general viability. The question addressed was whether there were differences in the *in vitro* toxicity of VPA and its metabolites that were related to the age of the livers from which the slices were taken. Liver slices from weanling rats were significantly more sensitive to VPA and its metabolites than the slices from livers of adult rats. The rank order of toxicities (4-en-VPA > VPA > 2-en-VPA) was the same in both sets of rat slices. The human liver slices were significantly affected by VPA and its metabolites, but these compounds were equal in

their ability to produce this toxicity. There was also an indication of differences in sensitivity to the toxicity of VPA in slices from livers of donors of different ages.
The MAH concluded that these nonclinical data do bring mechanistic hypothesis but do not bring new relevant safety information for paediatrics.

Rapporteur's comments:
The study further demonstrated the age-related sensitivity to the adverse effects of valproate. This sensitivity appears to be related to the stage of development of the metabolic capability of the rat. A similar age-related sensitivity to the adverse effects of valproate has been reported in paediatric patients and cited in section 4.4 of the SmPC.

CNS toxicity
Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci. 2003 May;993:103-14

The objective of this article was to investigate the following hypothesis: may antiepileptic drugs (AEDs) impair human intellect when given to treat seizures in infants and toddlers? In the immature rodent brain, suppression of synaptic neurotransmission via blockade of glutamate NMDA receptors or activation of GABA A receptors may trigger apoptotic neurodegeneration. This neurotoxic effect is limited to a developmental period characterised by rapid brain growth and active synaptogenesis.
Depression of synaptic neurotransmission is the common denominator in the action of AEDs. In this paper the authors investigated whether frequently prescribed AEDs may cause apoptotic neurodegeneration in the developing rat brain and what the underlying pathogenetic mechanisms are. Rats aged 3–30 days received phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, or valproic acid.
Histologic examination of the brains revealed that these drugs cause widespread and dose dependent apoptotic neurodegeneration in the developing rat brain during the brain growth spurt period.
In particular, valproate given at doses of 50 to 400 mg/kg on postnatal day 7 (P7) elicited apoptotic neurodegeneration in the developing rat brain in a dose-dependent manner. The threshold dose for valproate was 50 mg/kg and resulted in a peak valproate plasma concentration of 80 micrograms/mL which rapidly declined within eight hours. Higher valproate plasma concentrations correlated with increased severity of apoptotic brain damage. To determine how the apoptotic response to AEDs might differ as a function of developmental age, the authors administered either saline or valproate (400 mg/kg) to postnatal rats on P0, P3, P7, P14, and P20 and compared the neurodegenerative response in the infant brains at 24h following treatment with the response in P7 rats. A comparison of numerical densities of degenerating neurons in various brain regions of vehicle-treated rats with the densities of degenerating neurons in the same brain regions of valproate-treated rats was made. These experiments revealed that there is a time window from P0-P14 when various neuronal populations in the forebrain show transient sensitivity to valproate (data not shown in the published article).
The vulnerability period to the proapoptotic effect of AEDs coincides with the brain growth spurt period, which in the rat spans the first two postnatal weeks of life. In humans, this period begins in the third trimester of gestation and extends to several years after birth. Apoptotic neurodegeneration triggered by AEDs during this critical stage of development can at least partly account for reduced head circumference and impaired intellectual skills observed in pre- or postnatally exposed humans. This assumption leaves open the option that other mechanisms, such as impairment of migration or proliferation of neuronal progenitors, as well as disturbance of synaptogenesis, may also account for neurological deficits seen in humans exposed pre- or postnatally to AEDs.
This study presents further evidence of the potential for valproic acid to induce neurodegeneration for which the neonatal and juvenile rat demonstrates an increased sensitivity to. The SmPC cites adverse effects on several indices of CNS function observed predominantly in the paediatric population.

Rapporteur's comments:
This study presents further evidence of the potential for valproic acid to induce neurodegeneration for which the neonatal and juvenile rat demonstrates an increased sensitivity to. The SmPC cites adverse effects on several indices of CNS function observed predominantly in the paediatric population.

Chen J, Fangcheng C, Cao J, Zhang X, Li S. Long-term antiepileptic drug administration during early life inhibits hippocampal neurogenesis in the developing brain. J Neurosci Res. 2009 Oct;87(13):2898-907.

The objective of this article was to investigate the following hypothesis: may chronic administration of common AEDs during early life alters cell proliferation and neurogenesis in the hippocampus? In the present study, the authors investigated whether long-term administration of five AEDs, phenobarbital, clonazepam, carbamazepine, valproate, topiramate during early life influences neurogenesis in the dorsal hippocampus of the immature brain. To imitate the chronic administration of AEDs, which is typical in the clinical situation, rats were administered these drugs daily from P7 to P34 to ensure their exposure to AEDs during the entire ‘‘early childhood’’ period; a P7–10 rat central nervous system corresponds neurodevelopmentally to a full-term human neonate, and a P25–38 rat corresponds to a peripubertal child. With regard to the five AEDs, the authors did not find detrimental effects for carbamazepine, valproate, or topiramate on cell proliferation, survival, distribution, or differentiation in the dorsal hippocampus of the immature brain. In contrast, chronic administration of either phenobarbital or clonazepam had a harmful influence.
In this study, valproate was given to Postnatal day 7 (P7) rats at 250 mg/kg/day for 28 days. Bromodeoxyuridine was administered on P34 to label dividing cells. Cell proliferation was assessed 24 hr later, and cell survival and differentiation were assessed 28 days later. There were no changes in rats exposed to valproate at 250 mg/kg/day which corresponds to the following plasma exposure:

Table 1 Levels of VPA at 2 and 24 hours after administration on P7, P20 and P34 at 250 mg/kg/day

	P7		P20		P34	
In micrograms/ml	**2 hours**	**24 hours**	**2 hours**	**24 hours**	**2 hours**	**24 hours**
VPA (250 mg/kg/day)	58.4 ± 7.77	4.45 ± 0.77	64.4 ± 8.14	5.45 ± 0.79	62.4 ± 8.01	4.45 ± 0.77

IV.2.2.4 Discussion on non-clinical studies

Hepatotoxicity
In humans VPA is a known paediatric hepatotoxic agent due to the immaturity of the metabolic capabilities of the young population. The studies in the neonatal and immature rats showed a treatment related decrease in extramedullary haematopoiesis in the liver which was part of a general treatment related reduction of the organ weights of the lymphoid organs in the treated animals. The publication by Fisher 1994 also showed an increased sensitivity of the liver tissue of young rats to the toxic effects of valproate relative to the effects in the liver tissue from adult rats.

Severe liver damage, including hepatic failure resulting in fatalities in infants, mainly children under the age of 3 years, is addressed in the SmPC and it is likely that the rat findings reported in the published and company sponsored studies are representative of the effects observed clinically. An update to section 5.3 is not considered necessary as warnings regarding the severe hepatotoxicity of valproate in infants is addressed extensively in the special warnings section of the SmPC (Section 4.4)

CNS effects
The neonatal and immature rat IV studies showed CNS effects, i.e. reduction in absolute and relative brain weights, ataxia, decreased activity, loss of righting reflex, that were mild and transient at the low (30mg/kg/day) and intermediate dose (90mg/kg/day) and moderate to severe at the high dose of 240mg/kg/day. These CNS effects (e.g. severe neurological signs including sedation, ataxia, and tremor) were seen in adult rats at higher doses with a no-observed-adverse-effect level (NOAEL) of 90 mg/kg/day. The neonatal and juvenile rats are therefore more sensitive to the CNS effects of valproate than adult rats.

Summaries of two published studies were provided by the MAH in the clinical overview which showed conflicting results on the developing rat brain. The first study by Bittigau 2003 showed a dose dependant apoptotic neurodegeneration in the developing rat brain during the brain growth spurt period. The authors of the study investigated the time period for the susceptibility to the effect and identified postnatal days 0 to 14 to be the window of susceptibility of the neuronal populations in the forebrain to show transient sensitivity to valproate. This age group is equivalent to the third trimester of human pregnancy through to approximately ≥1 year. The second study by Chen 2009 investigated whether chronic administration of valproate alters cell proliferation and neurogenesis in the hippocampus in rats aged 7 days old to 38 days

(equivalent to the neurodevelopment of a full term infant human neonate through to a peripubertal child). Effects on cell proliferation, survival, distribution or differentiation in the dorsal hippocampus of the immature brain was assessed and no adverse effects on these parameters were observed.
The company sponsored juvenile studies in rats showed a reduction in absolute and relative brain weights and dose related CNS effects in the treated animals through the dosing period which could potentially be explained by a loss of neuronal populations as observed in the study by Bittigau 2003.

The MAH proposed 90 mg/kg/day as the NOAEL in the neonatal and immature rat study, however slightly decreased activity and ataxia were noted in immature rats given 30 and 90 mg/kg/day and in neonatal rats given 90 mg/kg/day. Although the central nervous system effects in these two groups were judged to be mild and transient, they are still part of a dose related adverse effect on the CNS. It is therefore considered that a NOAEL was not identified in the study in immature rats and 30mg/kg/day should be regarded as the NOAEL in the neonatal rat study. There is no toxicokinetic data available to calculate a safety margin in the case of the neonatal study or a margin of exposure to the effect dose in the immature rat study. A wide range of adverse effects on the CNS including those reported in the animal studies such as ataxia are cited in section 4.8 of SmPC. Some of the ADRs have been principally observed in paediatric patients. Findings, such as reduced brain weights, are not generally reported in the clinical sections of SmPCs.

CNS changes observed in the neonatal and juvenile rat studies were also observed in adult rats, although neonatal and juvenile rats seem to be more sensitive to these effects. CNS effects are already reported in the SmPC based on human (paediatric) data in SmPC section 4.8 and additional information on this in section 5.3 of the SmPC will be superfluous, and therefore is not needed.

Kidney
A reduction in the relative kidney weights and severe histopathology i.e. tubular mineralisation, dilated medullary tubules and increased incidence and severity of cystitis, were observed in the kidneys in the neonatal and immature female rat. These findings have not been observed in adult rat kidneys which could indicate an age-related susceptibility to the effects of valproate. The mechanism of toxicity is however unknown.
The MAH provided an expert review of the findings in the kidney by Harris et al (1974). The expert review concluded that the presence of these changes only in the immature female rats at dosages over 8 times that intended for clinical use reduces the risk in humans. However, without any toxicokinetic data to determine the safety margin based on a NOAEL this does not provide assurance. The expert review also suggested that the cystitis and secondary renal tubular dilatation observed in the neonatal rats may have been due to the mode of administration as it was not observed when administered via iv or orally to older rats and dogs. However, there were no reports of effects on the kidney in adult rats dosed via the intraperitoneal route in acute toxicity studies. Acute studies in adult dogs dosed i.p. did show changes within the peritoneal cavity as well as lesions to the gastrointestinal tract and mesentery indicating an irritating effect but no reported effects in the kidney.

After requested for additional data regarding urinary tract disorders and kidney disorders the MAH referred to two studies. In the juvenile rat study (TA91-003) a dose-responsive increase of tubular mineralisation and tubular basophilia was observed at the mid (90 mg/kg/day) and high dose (240 mg/kg/day) valproate in females only. No other effects on the kidney were observed. At the high dose, the effects were graded as mild and observed in presence of other more severe adverse effects in multiple organs, including mortality. In addition, these effects were neither observed in younger rats, nor in adult rats. The MAH cites a discussion of the National Toxicology Program, stating that mineralisation is more commonly associated with spontaneous and minute background findings of basophilic deposits and that these deposits in general have no pathological significance. As these effects were not accompanied by other adverse outcomes in the kidney, these effects are not likely to be of clinical significance.
In the neonatal study (TA91-004) slight to mild dilated renal medullary tubules was observed in both males and females at the high dose valproate only (240 mg/kg/day). In rats, nephrogenesis occurs after birth until PND11, tubular differentiation continues until the time of weaning (PND21), and functional maturity occurs at a later stage of development. In human, nephrogenesis is completed at week 35 of gestation, with postnatal maturation of the nephrons occurring during the first year of life. As renal development in the rat during PND4 and PND18 corresponds mostly with in utero development of the kidney in human, these effects are not likely to be of clinical significance within a paediatric context.

Other effects, including cystitis occurred at a very low frequency (n=1 per treated group) without a dose-response relationship, are not considered to be due to valproate treatment, and subsequently, of any clinical relevance.

Testes

Both neonatal and juvenile rat studies showed a treatment related reduction in the testicular weights of the treated animals. There were no corresponding reports of adverse histopathology in the male reproductive tract.

A significantly reduced testis weight was observed in both the neonatal rat and juvenile rat studies at 240 mg/kg/day valproate. No corresponding histopathological changes were observed. A reduction in testicular weight was also observed in an adult rat one-month repeat dose toxicity study, without any histopathological changes at the same dose level. At a higher dose level (480 mg/kg/day valproate), testicular atrophy was observed in adult rats. It should also be noted that the general adversity induced by valproate at 240 mg/kg/day was more severe in the neonatal/juvenile rats than in adults, but effects on testis remained similar.

Additionally, the MAH discussed the effects of valproate on male fertility in rats. In a fertility study in CD albino rats, male and female rats were treated before conception (male rats treated from 60 days before mating). Number of pregnant females was similar across all dose groups. However, at the highest dose (360 mg/kg/day) all pups did not survive up to day four. In a subsequent fertility study in a different strain of rats (Long Evans), only females were treated before conception. At 350 mg/kg/day, only 40% of the females became pregnant (compared to 95% of control). A different strain of rats was used for the subsequent study, which could have a different exposure profile. However, based on these data it can be concluded that effects on pregnancy rate were not due to effects of valproate on male rat fertility.

The data provided by the MAH confirms that findings on reduced testicular weight were also found in adult rats without accompanying histopathological findings in the testis at a similar dose level. In addition, no evidence of effects of valproate on male fertility were noted, and effects on female fertility were observed in a female fertility study for valproate where males were not treated with valproate. Section 4.8 of the SmPC for valproate states male infertility as an adverse reaction in human. Because of all arguments above, mentioning of the testicular findings in the juvenile rat population in section 5.3 of the SmPC is not of added value.

Retina

An increased incidence of retinal folds/rosettes was observed in the study in neonatal rats. This finding was not observed in the study in immature rats or ever recorded in adult rats. It is an effect that is likely due to a vulnerability arising from the stage of development of the eye in the neonatal rat.
The MAH discussed these findings: In the rat retina, photoreceptor formation takes place after birth and intensive mitotic activity has been observed in the neuroblastic layer of the retina during the first few days after birth (Percy DH, Albert DM., 1974). Thus, the finding of retinal rosette in the neonatal rat study but not in immature or adult rat studies with sodium valproate is probably attributable to the state of differentiation of the retina. Once differentiation has occurred, the retina is apparently no longer susceptible to the type of insult that leads to rosette formation. These findings indicate that the retinal lesions described were enhanced by valproate only when development of the neuroretina was incomplete. In rats, the degree of development of retina at birth has been compared to that of a 4-5-month human foetus rather than to that of a human newborn infant (Weidman TA, Kuwabara T., 1968). Children born to mothers receiving valproic acid during pregnancy were carefully studied, and the range of abnormalities noted did not involve the eye (Martinez-Frias LM, 1990).
Overall, the MAH considered the change in the eyes to be a minimal finding since it was not associated with inflammation, other intra-ocular abnormalities, abnormal differentiation or disorganization of the retinal layers and, all retinal layers were found in the retinal fold/rosette). However, the toxicological significance of the effect is unclear.

The MAH argues that the development of the human eye completes prenatally and on the basis of this, is only relevant to prenatal development, not the paediatric population and they submitted a review by Van Cruchten et al 2017 in support of this. However, the paper by Van Cruchten et al 2017 states the following which indicates that eye development completes postnatally and so the relevance to the paediatric population is not ruled out by this paper:

“The bulk of highly complex development of the retina occurs between GW24 and 3 to 4 months of age, when the optic nerve gets fully myelinated. Indeed, the new-born’s retina will be composed of the different layers as in adults, but still needs to mature (Smelseretal.,1974). At birth, the rod cells will be better developed than the cone cells. As a result, neonates primarily see shades of grey. Colour discrimination starts at 3 months of age when the cones mature”.

Retinal fold was observed in neonatal rats treated from PND4-PND18 at the highest dose tested (240 mg/kg/day valproate), where all pups of both sexes were affected (n=19/19). Incidence of retinal fold at the low and mid dose groups was comparable to control. The MAH states that retinal fold was not associated with inflammation, other intra-ocular abnormalities, abnormal differentiation or disorganization of the retinal layers and, all retinal layers were found in the retinal fold/rosette. It is agreed that for most of the eye related effects mentioned in the statement were not reported by the histopathologist, however, it was not specifically stated in the report that ‘all retinal layers were found in the retinal fold/rosette’. However, the absence of other histological effects on the eye can be considered reassuring.

Adverse effects induced by valproate on the eye, including retinal fold, have not been reported in immature rats (study TA91-003) nor in adult rats. Also there is currently no evidence available of inter-species concordance of effects to the developing eye by valproate, making it difficult to interpret the clinical relevance of this finding.

In addition, the MAH refers to a review concerning eye development across species, including human and rat by Van Cruchten et al. (2017), which states that development of the retina in rats is fully completed after birth at PND 14, at which all retinal layers are formed. Human retinal layers development is for the most part completed during gestation (GD240-280). It is agreed that therefore the retinal fold findings in rat are not relevant for the human paediatric population. However, as these findings in rat may be relevant for effects on eye development by valproate during pregnancy in human.

The retinal scars or folds observed in neonatal rats treated postnatally with valproate have not been exemplified in humans exposed *in utero* to valproate. Indeed, the cumulated weighted evidence based on the review of the Sanofi global pharmacovigilance data, of pharmacovigilance textbooks and of the scientific literature is insufficient to support an association between *in utero* exposure to valproate and retinal scars or folds in the offspring. The retinal scars or folds observed in neonatal rats treated postnatally with valproate have not been exemplified in humans exposed *in utero* to valproate. Indeed, the cumulated weighted evidence based on the review of the Sanofi global pharmacovigilance data, of pharmacovigilance textbooks and of the scientific literature is insufficient to support an association between *in utero* exposure to valproate and retinal scars or folds in the offspring.

Taken together all the currently available information on effects of valproate on the eye in juvenile and adult rats and, the absence of other histopathological findings in the eye in the neonatal study and the difference in timing of eye development between rat and human, the clinical relevance of the retinal folds observed in the neonatal repeat dose study are not considered relevant for the clinical paediatric population.

Next PSUR
At time of next PSUR, the brand leader MAH should submit a cumulative review considering information about retinal fold, retinal rosette/retinal coloboma, and coloboma in children after *in utero* valproate exposure. This request is incorporated in the broader request to the MAH to provide a cumulative review of ocular anomalies observed in children after *in utero* valproate exposure.

<u>Effects on lymphoid tissue/blood cytopenia</u>
Several effects on haematological parameters were reported in both studies. These effects included reductions in white blood cell and lymphocyte counts; reductions in absolute and relative organ weights of spleen, thymus, and adrenal were observed. Histopathological changes were reported in the bone marrow (decreased cellularity), liver (decreased extramedullary haematopoiesis), lymph nodes (lymphocyte depletion), thymus (lymphoid atrophy), spleen (white pulp atrophy and decreased extramedullary haematopoiesis). The MAH states that these effects are similar to that observed in young adult rats however the neonate and immature rats are more sensitive to the effect. The MAH did not discuss the clinical relevance of these findings, however section 4.8 of the SmPC does cite bone marrow failure (rare) and leukopenia (uncommon) which may be related to the effects observed in the juvenile rat studies.

Gross and histopathological findings such as the effects on the bone marrow etc. (data that are not usually obtained in patients) may be related to the effects reported clinically and indicate the underlying pathology involved.

The MAH argues that blood disorders and lymphoid tissue changes observed in neonatal and juvenile rats at 240 mg/kg/day were also observed in young adult rats. These effects seemed to be more severe in the neonatal and juvenile animals compared to (young) adult, as with the majority of the other adverse effects observed at the 240 mg/kg/day dose in. In addition, the MAH argues that based on a review by Everds et al. (2013), the changes observed regarding blood disorders and lymphoid tissue changes may be induced by stress secondary to the other observed adverse effects. Based on similar findings in adult compared to juvenile animals and the fact that wording on blood and lymphatic system disorders are mentioned in section 4.8 of the SmPC, changes to SmPC section 5.3 are not needed.

IV.3 Clinical aspects

IV.3.1 Introduction

MAH1 and MAH3 provided an overview of the main pharmacokinetic properties of valproate in paediatric patients based on relevant literature.

MAH1 submitted two unpublished MAH-sponsored studies. MAH2 conducted 6 non-interventional post-marketing surveillance studies, in which children were also included. The reports of the trials are in German, therefore summaries of the studies in English were provided. Study VPA 016/K was provided as a publication by Steinhoff BJ (1998). MAH4 submitted one paediatric MAH-sponsored study.

The MAHs also provided a large number of published studies (dating up to 2013), controlled and uncontrolled, and a number of reviews examining the efficacy of VPA in childhood epilepsy.

IV.3.2 Clinical aspects

IV.3.2.1 Pharmacokinetics

Absorption
Absorption of valproate is generally described as rapid and complete. In adults the mean absolute bioavailability of an oral formulation is in the order of 90-100% when compared to intravenous administration. The rate but not the extent of absorption is delayed if given with food (Guerrini R, 2006).
In paediatric patients the absorption rate of valproic acid varies with age. In neonates absorption is relatively slow with peak plasma concentrations (t_{max}) reached at ~ 4 h [range: 1h to 9h]. In infants the absorption rate is somewhat faster with tmax ~ 2 to 3 h [range: 0.5h to 6h]. In children absorption rate of valproate with tmax reached in ~ 1 to 2 h [range 0.5h to 5h] is comparable to that observed in adults (Morselli PL et al, 1980, Battino D et al, 1995). This could be explained by physiological differences with adults: neonates and infants undergo significant maturation changes in gastric and intestinal pH, gastrointestinal emptying time (Anderson GD, 2002).
The various formulations of oral valproate have different absorption profile. After oral administration of conventional capsule, uncoated tablet or liquid formulation, the time to reach the maximum plasma concentration (t_{max}) is approximately 1 to 3 hours. Enteric-coated tablets developed to avoid gastric irritation, delay tmax to 3 to 5 hours. With slow release formulations developed to reduce fluctuations in valproate plasma concentrations, valproate is absorbed more slowly (t_{max} > 5h) and maximum plasma concentrations (C_{max}) are 25% lower and plateaued between 4 and 14 hours.

Distribution
Protein binding
Valproate is extensively bound (85-95%) to plasma protein primarily to serum-albumin. The level of free fraction does not increase proportionally with total plasma concentrations demonstrating a saturable protein binding of valproate (Davis R et al, 1994). Some studies have shown similar protein binding and free fraction in paediatric patients (infants or children) as compared to adults (Herngren L et al, 1988,

Kodama Y et al, 1999, Cloyd JC et al, 1993, Panomvana Na Ayudhya D et al, 2006). Thus age has no effect on protein binding characteristics of valproate.
For low extraction ratio drugs in which clearance of the drug is dependent on protein binding and the activity of the metabolic enzymes, total concentrations will underestimate unbound or active concentrations. This is true for neonates and infants with decreased albumin concentrations (Anderson GD, 2010).

Volume of distribution
The apparent volume of distribution of valproate (Vd/F) tends to decrease with age. After a single dose the highest values of Vd/F are observed in neonates (0.3 to 0.4 L/kg) while Vd/F is around 0.2 L/kg in infants and 0.2 to 0.3 L/kg in children and 0.126 to 0.175 L/kg in adults (Davis R et al, 1994, Battino D et al, 1995). In adolescents and young adults (11 to 22 years) valproate volume of distribution is equal to 0.150±0.100 L/kg (Herngren L et al, 1988).
The apparent volume of distribution (Vd) ranges from 0.1 to 0.4 L/Kg, suggesting confinement principally to the circulation and extracellular fluid. VPA has been detected in cerebrospinal fluid (approximately 10% of serum concentrations), saliva (about 1% of plasma concentrations), and milk (about 1–10% of plasma concentrations). The drug crosses the placenta.

Metabolism
In humans valproate is metabolised almost entirely by the liver through at least five pathways with only 1 to 3% of the dose being excreted as parent drug in the urine. The two major pathways are direct glucuroconjugation of parent drug (50%) and mitochondrial β-oxidation (~40%) (Siemes H et al, 1993).
2-ene metabolite is pharmacologically active while 4-ene metabolite is involved in hepatotoxicity (Davis R et al, 1994, Keck PE Jr, 2002). VPA metabolites are excreted in urine. Small amounts of the drug are also excreted in faeces and in expired air. Results of studies in rats suggest the drug may undergo enterohepatic circulation.
Studies performed in paediatric patients lead to similar metabolic pathways in plasma or urine as those observed in adults (Battino D et al, 1995, Siemes H et al, 1993, Reith DM et al, 2000, Kreher U et al, 2001). As large inter-patient variability is observed, there are no differences between age groups in the recovery of metabolites. Only the proportion of daily dose recovered as valproate glucuroconjugate is smaller in children 10 years and younger than in older children.

Elimination
VPA is eliminated by first-order kinetics and has an elimination half-life of 5–20 hours (average 10.6 hours). In paediatric patients the systemic clearance of valproate varies widely with age.
Neonates have more variable and longer elimination half-life (t t1/2) ranging from 15 to 60 h. These values decrease in the first weeks of life, so that t1/2 values for infants approaches those in adults, i.e. 8 to 16 h (Morselli PL et al, 1980, Davis R et al, 1994, Battino D et al, 1995).
Infants younger than 2 months have a markedly decreased clearance of VPA compared with older children and adults, possibly because of delayed development of metabolic enzyme systems and an increased volume of distribution. In neonates, t 1/2, Vd and the percentage of unbound VPA are increased compared with values in infants or children. Mean half-life values vary considerably ranging from 17 to 40 hours in treated neonates. Elimination by glucuronidation only becomes fully effective by the age of 3-4 years.
In children aged 2-10 years receiving VPA, plasma clearances are 50% higher than in adults and lower t1/2 values are observed. VPA clearance decreases with increasing paediatric age, with children aged ≥ 10 years having PK parameters similar to those reported in adults (Davis et al., 1994; Guerrini et al. 2006; AHFS, 2013).

Population pharmacokinetics

From population pharmacokinetic studies performed in children, covariates influencing valproate clearance are: daily dose, body weight and/or age and co-medication as phenobarbital and carbamazepine depending on the model. Daily dose is a covariate taking into account the saturable protein binding. Anti-epileptic co-medications such as phenobarbital or carbazepine are well-known inducers of valproate metabolism. Body weight is found superior than age in some models, but body weight and age being closely related, can be considered as similar covariate identified in all studies (Yukawa E et al, 1997, Serrano BB et al, 1999, Bondareva IB et al, 2004, EL Desoky ES et al, 2004, Correa T et al, 2008, Jankovic SM et al, 2007, Jiang DC et al, 2007, Jankovic SM et al, 2010, Milovanovic JR et al, 2013).

Plasma concentrations of VPA

Plasma concentrations of VPA required for therapeutic or toxic effects have not been definitely established. Some reports indicate that therapeutic plasma concentrations may be 50–100 mcg/mL of total (bound and unbound) VPA and that concentrations in this range are maintained in most adults receiving 1.2–1.5 g of VPA daily. However, the possibility that some patients may be controlled with lower or higher plasma concentrations and that the free fraction of VPA increases with increasing dosage should be considered. The onset of therapeutic effects is several days to more than one week following initiation of VPA therapy. The relationship between dose and total VPA concentration is nonlinear; concentration does not increase proportionally with dose, because of saturable protein binding. The pharmacokinetics of unbound drug are linear.

Conclusion MAH

Elimination is the main pharmacokinetic parameter of valproate varying in function of age of children.
The ontogenesis of clearance mechanism may be the most critical determinant of a pharmacological response in infants and children. VPA elimination is decreased in newborns. Elimination by glucuronidation only becomes fully effective by the age of 3-4 years. In children aged 2-10 years receiving valproate, plasma clearances are 50% higher than those in adults. Over the age of 10 years, pharmacokinetic parameters approximate those of adults.

Rapporteur's comments:

The MAHs provided a comprehensive overview of pharmacokinetics of VPA in children and adequately addressed differences between the paediatric and adult populations and between different paediatric age subsets. An important aspect of the PK properties of VPA in children is the markedly decreased clearance in neonates and the increased clearance in children 2-10 years of age compared to adults. The SmPC of Epilim states, regarding PK properties of VPA in children: "The half-life of Epilim is usually reported to be within the range of 8-20 hours. It is usually shorter in children." This statement is not entirely accurate as differences in clearance and elimination half-life are noted in different paediatric age groups.
The MAHs were requested to provide text for paediatric specific PK information under a separate subheading "paediatric population" in section 5.2 of the SmPC. In order to more accurately highlight differences in elimination half-life, some additional wording have been added as follows:

SmPC, section 5.2

"Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults."

IV.3.2.2 Clinical efficacy

MAH sponsored studies

The MAH Sanofi-Aventis submitted two unpublished MAH-sponsored studies

1. *Multicentre comparative trial of Epilim (sodium valproate) and Tegretol (carbamazepine) in childhood epilepsy (Study GB 120 022.6.133) (1985-1990)*

This study was a randomised, open, multicentre comparative trial of sodium valproate and carbamazepine in the treatment of newly diagnosed generalised or partial seizures in children with epilepsy (63 centres in the UK). A total of 260 children aged between 4 and 15 years were included and randomised in two groups of 130 children each. In one group, sodium valproate was to be taken twice daily at 12-hour interval. The scheduled regimen began at 200 mg twice daily with incremental changes of 200 mg/day at the investigator's discretion until control of seizures has been achieved. The daily dose was not to exceed 30 mg/kg. In the other group, carbamazepine was to be taken in divided doses in accordance with the investigator's normal practice. The scheduled regimen was 5 mg/kg/day in divided doses, increasing to 10 mg/kg/day after the second week. Further increases were to be made at the investigator's discretion until control of seizures has been achieved. The daily dose was not to exceed 20 mg/kg. Patients were assessed at 1, 3, 6 and 9 months after entry and after 1, 1.5, 2 and 3 years of treatment. Efficacy and safety assessments were carried out at each visit.
The endpoints of the trial were:

a) Poor control. Patients who continued to have seizures with a serum level in the upper part of the therapeutic range were regarded as treatment failures
b) Severe adverse events. Patients were classed as treatment failures if they had side effects of sufficient severity to warrant discontinuation of their current treatment.

Efficacy was assessed in 3 ways: Analysis of the endpoints (treatment failures), remission analysis (time to achieve specified period of freedom from seizures) and retention analysis (time remaining in trial on randomised treatment).
Patients who were regarded as treatment failures on one drug were then switched to the alternative anticonvulsant and followed up for the remainder of the 3-year treatment period. Patients who failed on both trial drugs were also followed up for the full 3-year period wherever possible. No other anticonvulsant medication was allowed and if deemed necessary, the patient was classed as treatment failure but was followed up for the whole study duration if possible.
The analysis of efficacy data showed no difference between treatments in terms of endpoints, with 88% of patients on sodium valproate and 88% of patients on carbamazepine still in the study at 6 months. At 3 years, 66% of patients were still on randomised treatment or had recently stopped treatment after achieving full seizure control.
For remission, no overall statistically significant differences between treatments were detected for the 6, 12 and 24-month analyses. However, the 24-month analysis showed an advantage to sodium valproate which approached statistical significance (Relative Risk (RR) 1.44; 95% confidence interval (CI): [0.93-2.21]; p=0.10). Regarding remission as a binary variable (Yes/No), the 6-month data indicated no statistical difference between treatments (p=0.78), with 77% versus 79% of patients achieving remission on sodium valproate and carbamazepine, respectively. Both drugs achieved a high degree of seizure control, 75-80% patients having at least 12 months freedom from seizures and 40-60% at least 2 years.
Overall, the authors concluded that the two treatments were similar in efficacy.
Treatment was withdrawn because of adverse effects in 12% of the patients on carbamazepine and 15% of the patients on valproate. Carbamazepine treatment appeared to be associated with a higher incidence of dizziness, vision abnormalities/diplopia, abnormal gait/ataxia, insomnia and rash. Patients on VPA reported a higher incidence of appetite increase, weight increase, alopecia and possibly nausea, concentration impairment and paradoxically anorexia. No unexpected safety findings were observed.

2. *Study of the efficacy and tolerability of sodium valproate (LA 40220 SRF) in the treatment of partial seizure and generalised epilepsy (Study P.1488 and P.1489; report n°491.6.032) (1989-1991)*

This study was an open, non-comparative, monocentric study in out-patients treated for 6 months (partial seizures) to 12 months (generalised epilepsy) and with minimal assessments at 0, 1, 3, 6 months and when applicable 9 and 12 months. Assessment criteria:

a) Efficacy: number, chronology and type of seizures were recorded.
b) Safety: all observed and reported adverse events were recorded.

16 patients with partial seizures aged from 18 to 41 years and 12 patients with generalised epilepsy aged between 14 and 28 years were included. Due to the low population of paediatric patients, the efficacy of sodium valproate was not evaluated in this population.

Rapporteurs comments:
Study P1488/P1489: This study included an unspecified but low number of children and therefore efficacy was not evaluated in the paediatric population. Adverse events were mild and no unexpected safety findings were reported.
Study GB 120: The primary endpoint of this study is treatment failure which is influenced both by differences in efficacy and safety. For this endpoint, similar efficacy between the two drugs was shown. Considering limitations of this old study such as the open label design, the potential for misclassification of seizure type and insufficient power to detect differences in the drugs' effects in different seizure types, no robust conclusions regarding the comparison between the two drugs can be drawn.
No new safety concerns are identified.

MAH Desitin Arzneimittel GMBH conducted 6 non-interventional post-marketing surveillance studies, in which children were also included. The reports of the trials are in German, therefore summaries of the studies in English were provided. Study VPA 016/K was provided as a publication by Steinhoff BJ (1998).

1. *VPA 016/K: Antiepileptic pharmacotherapy with sustained release sodium valproate, Steinhoff BJ, Ces.a Slov.Neurol.Neurochir., 61/94, 1998, No.6, p.291-295*

A 3-month post marketing surveillance study investigated the efficacy and tolerability of the sustained release sodium valproate formulation (Orfiril retard) in 366 patients with primary generalised or focal seizures. 137 patients were under 19 years of age. 87 patients were newly diagnosed drug naïve patients, 116 patients had received prior antiepileptic treatment other than valproate and 163 patients were receiving conventional valproate preparations. The seizure frequency was reduced and the number of seizure-free patients increased in all subgroups during the observation period. Nearly 80% of the drug-naïve patients became seizure free after 3 months of treatment. The incidence of adverse events (16%) was lower than under previous therapy. The authors concluded that sustained release valproate can be initially introduced successfully in newly diagnosed patients; patients under conventional valproate therapy may be switched to the same daily dose of sustained release valproate which is administered in a more convenient twice or once daily regimen.

2. *VPA 024/K: Post-marketing study with Orfiril injection solution (1998)*

A prospective multicentre, non-comparative, post-marketing study was conducted to document the use of Orfiril Injection Solution (sodium valproate) in 167 treatment episodes (total 384 administrations) for neurologic (n=45), neurosurgical (n=36) and psychiatric (n=7) disorders and in replacement therapy and interval treatment (n=79). Replacement therapy and interval treatments were carried out particularly often in children (81.8% of all episodes in the patients aged up to 12 years). The study participants were aged between 6 months and 83 years (median = 22 years); 55 patients were between 0-12 years of age. It is not clear from the study report how many patients were 13-18 years of age. A dosage of 20 to 30 mg/kg body weight was used in children. Orfiril Injection Solution was administered as a bolus, as infusion therapy or as a bolus followed by infusion. The treatment objective was achieved completely in 141 (equivalent to 84.4%), partially in 15 (9.0%) and not at all in 11 (6.6%) of the 167 documented episodes.
Children showed a higher rate of completely successful treatment than the total sample (up to three years of age: 100%; up to 12 years: 96.4%, i.e. 53 of 55 episodes, respectively). The highest success rate was observed for replacement therapy and interval treatment. These two factors, however, are considerably confounded with each other (replacement therapy or interval treatment were mainly documented for children of this age group) and therefore, it cannot be conclusively established which of the two factors is primarily linked to a high success rate. The lowest success rate (42.9%) and the highest non-responder rate (also 42.9%) was observed for psychiatric disorders for which, however, there were only 7 documented episodes.
During the surveillance period a total of 16 adverse drug reactions occurred in altogether 8 treatment episodes (4.8% of 167), only 3 of which – injection site reaction, nausea and tiredness – were reported more than once. None of the ADRs reported were classified as serious or unexpected. 5 mortalities occurred during and after the treatment, the drug surveillance study, none of which was considered to have a causal relationship with Orfiril.

3. *VPA 029/K: Post marketing study with Orfiril long (2000)*

For this study data were provided for 194 children aged 12 years or less. Prior to inclusion in the study: 50 children received no AED treatment, 96 received an AED monotherapy, 34 were on 2 AEDs and 8

children were on 3 or more AEDs. More than 50% of patients had been treated with valproic acid formulations other than Orfiril long. The children suffered from various seizure disorders.
In 100 patients (69.9% of the 143 patients with prior seizures), a reduction in seizure frequency of 50% or more was observed (8-week observation period). An increase in seizure frequency was observed in 13 patients (6.7%). 10 adverse events were noted in 7 patients (3.6%) and in 10 patients treatment with Orfiril long was terminated.

4. *VPA 032/K: Post marketing study with Orfiril 300 retard (2001)*

Data were documented for 840 patients between 2-98 years of age, who were newly stabilised to Orfiril 300 retard. Roughly half of the patients were 16 years old or younger. 597 patients suffered from primary generalised seizures and 309 from focal seizures. 70% of the patients had received antiepileptic drugs before starting treatment with Orfiril. Nearly half of the 840 study participants had received another valproic acid preparation before. Following a baseline examination at the start of treatment with Orfiril 300 retard, 3 follow up visits were scheduled at monthly intervals. The seizure frequency per 4 weeks decreased by an average of 76%±43.6 (mean±SD) for primary generalised seizures and by 72.8%±40.5 for partial seizures. The decreases in seizure frequency were more pronounced in children under 13 years of age (primary generalised seizures: -81.5%; partial seizures: -77.0%), who also had a higher seizure frequency at pre-treatment. From the first follow up visit on, more than 50% of the patients were entirely seizure free. During treatment with Orfiril 300 retard, 168 adverse events were reported in 156 patients (18.6% of 840). The most frequently observed AE was somnolence, followed by impaired concentration and nausea.

5. *VPA 041/K: Post marketing study with Orfiril long as once a day evening dose*

359 patients aged 12-86 years (mean age: 37.5) participated in this study (6 patients were younger than 12 years and they were not included in the analysis). 71% had generalised seizures. Patients were switched to the once-a-day evening dose of Orfiril long. A total of 87.0% had received a product containing sodium valproate before the change of medication; 34.5% of cases had received a non-sustained release form of valproate, 23.4% a sustained-release form of valproate and 15.0% of patients had already received Orfiril long twice a day previously. Among the 220 patients with convulsions at the start of the observation, the frequency of seizures decreased in 92.7% of cases and 62.3% of patients were seizure-free at the end of the observation phase. Adverse events (AE) in which a relationship to Orfiril long could not be excluded were documented in 14 patients (3.9%). None of the total of 20 AEs was classified as serious.

6. *VPA 044/K: Post marketing study with valproate sustained release minitablets once daily in the evening*

The data of this non-interventional trial were directly extracted from the physician's electronic patient database. The observational period was 7 weeks compared to a retrospective period 7 weeks before start of the study. 82 patients were included in this trial. The patients were naive to treatment or changed from another antiepileptic or valproate preparation to valproate sustained release minitablets once daily in the evening. After conversion to valproate sustained release minitablets once daily in the evening 40% of the patients became seizure free. Of the 41 patients with at least one seizure during the beginning period, 39 had a seizure reduction of more than 50%. The mean number of seizures decreased from 1.6 to 0.6 during the observational period. 4 patients terminated the study prematurely.

Rapporteur's comments:
In the studies above, efficacy and safety were assessed in terms of seizure frequency and AE frequency. Limited conclusions can be drawn based on the efficacy results from these non-interventional trials; the studies are open label, non –controlled and details on baseline characteristics of the samples and efficacy and safety endpoints are lacking. No new safety information relevant to the paediatric population is identified in these reports

MAH ICN Polfa Rzeszow S.A. (now PharmaSwiss Ceska Republika s.r.o.) submitted one paediatric MAH-sponsored study.

1. *Clinical comparative evaluation concerning the efficacy, tolerance and toxicity of the preparations Dipromal and Depakine, in the treatment of epilepsy in children (Poland, 1985-1986)*

60 children aged 2 to 17 years were included in the study. 40 children were previously ineffectively treated with various anticonvulsant combinations. Patients were randomised into 2 groups: group I (30 children) received Dipromal and group II (30 children) received Depakine. Both drugs in the form of 200 mg tablets were administered at 10 – 40 mg/kg daily in three divided doses. Children with primarily generalised, non-epileptic and mixed seizures (31 cases) made up the higher number of patients in both groups, with significantly lower number of patients with simple partial seizures – 12 cases. Laboratory studies were performed before the beginning of treatment and after 1 and 3 months of drug administration. EEG studies were performed before, and after 3-month treatment period. After at least 4 weeks of treatment, in all children treated with Dipromal, drug level was determined before and 2 hours after its administration.
The observation period varied from 6 to 12 months. Results/Authors conclusions: Best results were achieved in primarily generalised seizures, epileptic and nonepileptic, while the worst results appeared in case of simple partial seizures, secondarily generalised as well as partial seizures with complex symptoms. Both drugs, at therapeutic doses, showed rapid and effective influence on basal and seizure activity. There were no significant differences between the use of Dipromal and Depakine on VPA plasma concentrations. Dipromal showed relatively good clinical tolerance and low toxicity.

Rapporteur's comments:
This study provided evidence of similar bioavailability, efficacy and tolerability between the two different VPA preparations.

Published studies
In addition, the MAHs provided a large number of published studies (dating up to 2013), controlled and uncontrolled, and a number of reviews examining the efficacy of VPA in childhood epilepsy.

Rapporteur's comments:
Following two European referrals, valproate is now contraindicated in pregnancy unless there is no suitable alternative treatment and in girls and women of childbearing age unless the terms of a special pregnancy prevention programme are met.
The MAHs submitted studies examining the efficacy of VPA in children or in adults and children, in different types of seizures and epileptic syndromes, as monotherapy and as part of a polytherapy regimen, in newly diagnosed patients and patients treated previously with other AEDs. Most studies submitted were non-comparative, prospective and retrospective, that provided some evidence of the efficacy of VPA in achieving either complete control of seizures or seizure reduction in paediatric patients. In many of these studies, the authors concluded that VPA was more efficacious in generalised epilepsy compared to partial epilepsy. Considering the inherent limitations of these studies, they provide some evidence for the efficacy of VPA in various types of seizures occurring during childhood.

A number of randomised controlled paediatric studies were also submitted. VPA had equal effects in the control of different seizure types with other drugs such as ethosuximide, lamotrigine, phenobarbitone, carbamazepine. The MAHs also submitted a number of systematic reviews on VPA where studies examining its efficacy and safety in both children and adults were discussed.

Status Epilepticus:
VPA, as an IV injection, is indicated as replacement therapy in patients temporarily unable to take the drug orally. However, VPA as an IV injection is also used off label in clinical practice in children presenting with status epilepticus (SE). The MAHs submitted studies examining the efficacy of VPA in the management of convulsive and non-convulsive SE. Most of these studies were prospective or retrospective, open label, uncontrolled studies in small numbers of children and in many cases with not very well-defined primary endpoint. The results from these studies are positive and show that VPA has potentially a role in the management of SE. In a systematic review (Trinka E et al., 2014) of the efficacy and safety of IV VPA, randomised and non-randomised trials in adults and children were discussed. The authors concluded: "The published experience is consistent with VPA being a safe and effective therapeutic option for patients with established SE who have previously failed conventional first-line treatment with benzodiazepines, but high-quality randomised controlled trials are needed to inform clinicians on its comparative effectiveness in SE." A Cochrane review of anticonvulsant therapy for SE (Prasad M et al, 2014) reviewed a very small number of studies with VPA and did not come to any definite conclusions regarding its efficacy compared to other AEDs. The review also identified that there are areas

that require attention in future research, such as acceptable definitions of premonitory, early, established and refractory status epilepticus and agreement on the definition of outcomes.
The position of VPA in the management of paediatric SE is not fully established at present.
In conclusion, no new data regarding VPA's efficacy in the management of seizures in childhood were identified.

MAH Sanofi-Aventis submitted a number of published studies in children with bipolar treated with VPA.

Rapporteur's Comments:
VPA is used off label for the management of bipolar disorder (BD) in children.
Most of the studies submitted were open label uncontrolled studies and therefore limited information regarding the efficacy of VPA in childhood BD can be derived. Other limitations found in some of these studies are small number of paediatric patients, lack of clear description of inclusion criteria, lack of clear definition of response and inadequate duration of treatment to test for maintenance of effect.
VPA failed to show superiority in two randomised placebo-controlled trials in children (Findling et al., 2007, Wagner et al. 2009) and also was not found to be superior in a randomised trial when compared to quetiapine (Delbello et al, 2006).
A recent systematic review (Davico C et al, 2018) of anticonvulsants for psychiatric disorders in children and adolescents, found that for the treatment of BD, VPA showed no evidence of superiority over placebo in 3 RCTs, and was inferior to risperidone based on 4 RCTs.
Overall, the studies reviewed did not provide robust evidence for the efficacy of VPA in acute mania in children.
The submitted data do not warrant any changes to the current paediatric indications of VPA for children.

IV.3.2.3 Clinical Safety

MAH1 provided a review of their global pharmacovigilance database (since the valproate launch until 31 January 2013), a review of the safety part of the efficacy trials, and a literature search of safety studies concerning valproate in the paediatric population. The cases reported in context of exposure during pregnancy or during lactation were excluded from the analysis.

<u>From the pharmacovigilance experience</u>

- Based on 3730 medically-confirmed cases (92 solicited and 3638 unsolicited since the first case entered into the database until 31 January 2013) recorded in children aged less than 18 years in the Sanofi pharmacovigilance database, the most frequently involved system organ classes (SOCs) (representing more than 10% of cases in post-marketing experience) were Nervous (29.9% of cases), Investigations (25.6%), General (22%), Gastrointestinal (19.3%), Skin (17.7%), Blood (14.0%), and Metabolism (10.3%). In these SOCs, the most frequently reported ADRs were convulsion and sedation/somnolence, aspartate aminotransferase/alanine aminotransferase increased and drug level increased, drug interaction and drug ineffective, pancreatitis and nausea/vomiting, rash and alopecia, thrombocytopenia, and hyperammonaemia respectively. All these reactions are listed in the Company Core Safety Information (CCSI).
- Overall cases were mainly reported in the children [24 months-12 years] and in the adolescent [12-18 years] groups, representing 52.6% and 33.2% of cases, respectively. This is in accordance with the sales recorded, which concerned more these 2 age-groups, with predominance for children group.
- With respect to the important risks identified for valproate (severe liver damage, acute pancreatitis, suicidality, exposure during pregnancy, serious skin disorders, blood cytopenia, extrapyramidal disorders, sedation, osteoporosis, and drug interaction with carbapenem drugs): all of them concerned more the children group [24 months-12 years], and then the adolescent group [12-18 years], except the reaction suicidality which concerned more the adolescent group.
- Some cases (4.5%) were reported in children treated for bipolar disorders, although this indication is not supported by the MAH. The safety profile is comparable to that of epilepsy indication, except suicidality which appears relatively more reported.
- A fatal outcome was reported in 190 cases (5.2% [190/3638]). Among these cases, valproate was indicated for epilepsy in 145 cases, and for bipolar disorders in 3 cases. Valproate was orally administered in 103 cases, and no injectable form was received. The causes of death were most

frequently reported in the Hepatobiliary disorders SOC (24.2% [46/190]) and representing 1.3% among all cases (46/3638). This is in line with the information provided in the Warnings and Adverse reactions sections of the CCSI. A fatal outcome was more reported in the group of children [24 Months – 12 years].

Published studies

A large number of published studies were submitted by the MAHs.
MAH1 concluded:

- VPA was generally well tolerated in children in clinical trials; most adverse events were mild and transient. VPA was commonly associated with weight gain, appetite increase, somnolence, alopecia and gastrointestinal symptoms. Hypofibrinogenaemia, elevated liver enzymes and thrombocytopenia were relatively common when higher doses of VPA were administered. Hypothyroidism, often subclinical, a decrease in bone mineral density and a change in lipid profile, which could be related to weight gain, were also observed.
- The vast majority of the adverse reactions reported has also been reported in adults and are mostly listed in the CCSI.
- The tolerability of valproate in the paediatric population would appear to be very similar to that in adults, suggesting that the same precautions be taken when administering to children, although particular attention should be paid to potential liver and pancreas toxicity, since young children (particularly those <3 years of age for liver risk) are considered to be at higher risk of this complication.
- Abnormal behaviour/aggression/agitation/disturbance in attention/psychomotor hyperactivity/learning disorder were mentioned as mainly observed in paediatric patients.

The MAH concluded that no new safety signal was identified in the paediatric population. The MAHs also submitted relevant PSUR data or referred to PSURs which have already been submitted and assessed.

Discussion on clinical safety

Post marketing data and published safety studies
The MAHs reviewed post marketing data and conducted a literature review in search of any new safety information relevant to use in the paediatric population. The major safety concern with the use of VPA in children is the risk of severe liver dysfunction and hepatic failure. The findings of this review largely confirm the known safety profile of VPA in children.

Additional safety information
A number of studies have reported biochemical changes reflecting metabolic and endocrinologic abnormalities associated with weight gain in children receiving VPA; In some studies (Tokgoz et al, 2012, Sonmez FM et al, 2013, Kanemura H et al, 2012, Hamed SA et al, 2009) increases of leptin, insulin, neuropeptide Y (NPY) levels and decreased ghrelin levels were observed. Other studies did not find changes in insulin or glucose concentrations (Abaci A et al, 2009). Lipid abnormalities, including increase in total cholesterol and low-density lipoprotein, have been reported (Abaci A et al, 2009). Other studies did not confirm these findings (Nam SO et al, 2011, Tomoum HY et al, 2008). The exact pathogenesis of weight gain, the importance of these metabolic derangements and their contribution to the risk of metabolic syndrome and long-term cardiovascular risk are currently unknown.
The SmPC already mentions the following in sections 4.8: weight increased, obesity.
The safety topics dyslipidaemia and metabolic syndrome have been reviewed in the latest PSUR (covering the period 24 January 2015 - 23 January 2018) and it was concluded that information at this stage is limited to support a casual association. MAHs will continue monitoring these safety issues.

VPA treatment has been associated with serum carnitine depletion in paediatric epileptic patients (Anil M et al, 2009, El Mously S et al, 2018, Qiliang L et al, 2018, Fukuda M et al, 2015). In most cases presented in these series, patients with carnitine deficiency were asymptomatic but there are case reports where it is associated with asymptomatic hyperammonaemia and hyperammonaemia encephalopathy. Carnitine deficiency is reported to be relatively common in epilepsy and other factors apart from VPA therapy, play a role such as underlying metabolic diseases, nutritional inadequacy, and treatment with other AEDs. The weight of each factor in the development of carnitine deficiency in children with epilepsy is not clear.

L-carnitine supplementation has been used for the treatment of VPA-induced hepatotoxicity and hyperammonaemic encephalopathy. It is postulated that carnitine supplementation may increase the beta-oxidation of VPA, thereby limiting cytosolic omega-oxidation and the production of toxic metabolites that are involved in liver toxicity and ammonia accumulation (Lheureux PE, et al, 2009). A systematic review (Perrott J et al, 2010) evaluating the use of l-carnitine for the management of VPA overdose in humans concluded that the evidence supporting its use is limited and that more rigorous studies are needed. However, the authors considered that it would be reasonable to consider l-carnitine for patients with acute overdose of VPA who demonstrate decreased level of consciousness. The current advice for VPA overdose in Toxbase includes the following: "Consider giving L-carnitine to patients who have taken a large valproate overdose and have coma, hyperammonaemia or hepatotoxicity or a valproate concentration greater than 450 mg/L." and "L-carnitine is recommended in cases of severe valproate toxicity but its role in hastening recovery of unconsciousness has not been established."
Glatstein M et al (2017) reviewed medical records of paediatric patients presenting with VPA-induced hyperammonaemic encephalopathy and concluded that intravenous L-carnitine, at a dose of 100 mg/kg/d in 3 divided doses each over 30 minutes is a safe and effective treatment in the management of VPA in children.
In conclusion, there is some evidence from case reports/small case series that l-carnitine could be useful for the management of VPA induced toxicity, however controlled studies confirming its efficacy are lacking. The MAHs should continue monitoring available literature regarding use of l- carnitine and if further robust data for its use in VPA toxicity become available, propose updates for section 4.9 overdose of the SmPC.

Juvenile animal studies and Clinical experience
Dose-related serious adverse effects on the CNS, retina, testes, liver, kidneys, and haematopoiesis were observed in the 2 submitted juvenile animal studies. The neonatal and juvenile rat exhibited increased sensitivity relative to adult rats.

Hepatobiliary disorders are well known and described in detail in the SmPC as is the particular increased risk for children below 3 years of age.
The clinical literature data submitted by the MAHs confirmed that effects from the hepatobiliary, CNS and blood systems occur commonly in the paediatric population.

To further explore how the non-clinical studies' findings translate into clinical experience, a search in the MHRA Yellow Card database was conducted to identify all ADRs submitted for children 0-18 years of age, from July 1963 until December 2018 for the following MedDRA system organ classes (SOCs): Nervous, Eye, Renal, Blood and Lymphatic, Reproductive and Breast disorders. Effects attributed to transplacental exposure to VPA are mentioned separately as these have been assessed extensively during the Article 31 European referrals.

- Central nervous system and psychiatrics effects

Non-clinical
A number of CNS effects are mentioned in the SmPC and some of them are mentioned with higher frequency in the paediatric population.
The safety of sodium valproate on neurodevelopment *in utero* has been extensively investigates during the European reviews under Article 31 of Directive 2001/83/EC . Whilst CNS development commences prenatally it continues postnatally, up to adulthood and therefore the inherent susceptibility of the developing nervous system to the adverse effects of sodium valproate following intrauterine exposure should also be considered relevant to the direct exposures associated with the paediatric indication.
Valproate inhibits neurotransmission and this action could be linked with adverse effects on the developing nervous system. The MAHs should continue monitoring CNS and psychiatric adverse effects in children and propose updates to the SmPC if new paediatric specific information becomes available.

Clinical
481 cases, out of which 212 with ADRs after transplacental exposure. Almost all of the remaining cases concern ADRs mentioned in the SmPC, such as seizures (uncontrolled/breakthrough/prolonged/status epilepticus/loss of efficacy) (N=124), encephalopathy/coma related to hepatotoxicity/hyperammonaemia (N=24), somnolence (N=26), tremor (N=16), headache (N=9), lethargy (N=5), ataxia/balance disorder

(N=9), aggression (N=8), hyperactivity (N=12), abnormal behaviour (N=6), disturbance in attention (N=4), paraesthesia (N=2), extrapyramidal disorder (N=2), cognitive disorder (N=1), agitation (N=1).
Further ADRs identified:

- More specific movement disorders were also reported: hyperkinesia (N=4), dystonia (N=2), opisthotonos (N=1), oculogyric crisis (N=1), chorea (N=1).
- Speech disorder/dysarthria (N=4).
- Personality disorder (N=4)
- Drooling (N=2)

The specific movement disorders overall fall under the general term “extrapyramidal disorder” which is mentioned in the SmPC.
For the remaining ADRs, although causality with the use of valproate cannot be excluded, the data are inconclusive due to low number of cases, information for a number of those is incomplete and confounders such as underlying or intercurrent illness and use of concomitant medications exist.

Although there is no need to update section 5.3 regarding CNS changes, the preclinical findings of “loss of righting reflex” and “decreased activity” in juvenile rats were reason for the MAH to review paediatric cases in MAH’s safety database reporting reflex disorders. Ataxia was also reported in juvenile rats, but this adverse reaction is already included in SmPC 4.8 and it is therefore accepted that cases with ataxia were not included in MAH’s search.

Regarding “loss of righting reflex” as seen with valproate in juvenile rates, postural reflex impairment seems to be the most appropriate term to search for in MAH’s database. However, no such cases were found. For the 11 cases reporting reflexes abnormal, hyporeflexia, and/or areflexia the MAH considers that the clinical situations in which these events occur (e.g. in the context of hyperammonaemia or overdose) did not exactly match to what was observed in the non-clinical studies.
No new safety information was identified regarding above reflex disorders in paediatric patients with valproate use.

A total of 53 cases have been reported up to 31 March 2019 by MAH1. Cases reported muscular weakness in the context of epilepsy or listed reactions with valproate were excluded from further analysis (n=8), which is agreed as muscular weakness can be considered in these cases to be a secondary event.
The causal role in the 4 strongest cases (including one case of facial muscular weakness) was assessed as possible by MAH1, but mainly based on a plausible temporal relationship. Valproate was reported to be discontinued in three patients with outcome recovered with or without sequential treatment, respectively. Remaining eight cases reported no reasonable time to onset of the event of muscular weakness or a negative de-challenge or were considered to be confounded by other medications or comorbidities. A possible causal relationship between muscular weakness and valproate use was assessed in a limited number of paediatric patients. MAH2 performed a search of MAH’s pharmacovigilance database for PT Muscular weakness and revealed 13 cases, thereof 2 cases occurring in children and 3 cases in adolescents. Taking into account these case reports, data is considered insufficient to draw any conclusions on causal relationship between muscular weakness and valproate treatment in children.

Regarding hypotonia, In a large number of the 34 identified cases, the event of hypotonia occurred in the context of listed reactions for valproate including overdose, hyperammonaemia, and (hyperammonaemia) encephalopathy. In two cases the causal role of valproate was assessed as possible. In the first patient carnitine deficiency related to valproate may explain the event of hypotonia and the second patient was not considered to be epileptic after all and recovered from hypotonia after discontinuation of valproate (while oxcarbazepine and levetiracetam were discontinued at the same time). The remaining cases reported no reasonable time to onset of the event of hypotonia, other explaining causes, or provided no detailed information (based on which proper causality assessment was not possible). In just 2 post-marketing cases there may be a possible causal relationship between hypotonia and valproate use, based on which no firm conclusion can be drawn. Based on the available data a relationship between valproate us in children and the development of muscular weakness or hypotonia cannot be concluded. The MAH’s conclusions that there is no need to update SmPC section 4.8 regarding muscular weakness and hypotonia can be supported.

Eight cases were identified, but all reported an alternative explanation for the occurrence of events and a causal role of valproate may be less likely.

Most cases of coordination abnormal/developmental coordination with valproate use in paediatric patients MAH1 presented were considered to be confounded. Even 3 out of the 4 strongest cases identified by MAH1, reported concomitant medication and/or underlying morbidity that may have contributed to the events. Several cases were poorly documented and did not allow proper causality assessment.
A search pharmacovigilance database of MAH2 for PTs coordination abnormal and developmental coordination disorder revealed 13 cases of coordination abnormal, thereof 3 cases occurring in children. No cases of developmental coordination disorders were identified. Closely related terms ataxia and dizziness are already listed for valproate and might not be clearly distinguishable from coordination disorders. None of the cases provide conclusive evidence for a causal relationship between coordination disorders and valproate treatment. They are either poorly documented with unclear temporal relationship between valproate and coordination disorder or report alternative explanations for occurrence of coordination disorders.
Based on the available data a relationship between valproate use in children and coordination abnormal/developmental coordination cannot be concluded. There is no need to update SmPC section 4.8 regarding coordination abnormal/developmental coordination disorder in children treated postnatally with valproate.

- Renal and urinary disorders

Non-clinical
urinary incontinence, renal failure, enuresis, tubulointerstitial nephritis, and reversible Falconi syndrome are mentioned in section 4.8. No new information relevant to the paediatric population was identified in the submitted data.

Clinical
62 cases, out of which 27 refer to ADRs after transplacental exposure. The remaining cases are: renal impairment/failure (N=10), mostly associated with sepsis or multiorgan failure or necrotising pancreatitis or prolonged convulsions/status and disseminated intravascular coagulation; Fanconi syndrome/renal tubular acidosis (N=15); incontinence (N=5), UTI (N=1), nephrogenic diabetes insipidus (N=1) and diabetes mellitus/polyuria (N=1)
The above except for the last 2 are mentioned in the SmPC. No new safety signal was identified in these cases.

- Eye disorders

Non-clinical
Diplopia is mentioned in the SmPC. MAHs submitted two studies reporting on ophthalmologic results from children treated with VPA. Verrotti et al (2004) reported that after 1 year of treatment with VPA epileptic adolescents exhibited deficits in colour vision and that further investigations were required to determine the pathophysiological basis for these alterations. The same group of patients (Lobefalo L et al, 2006) was further evaluated by using optical coherence tomography and no modification of retinal nerve fiber layer and macular thickness parameters was found. Therefore, the finding of impairment of colour vision was not explained by an alteration of retinal structure. Similar deficits in colour vision were found in adults (Sorri I et al, 2005), but the authors considered them to be subclinical and not requiring monitoring. According to the optical coherence tomography measurements, the average and superior peripapillary retinal nerve fibre layer thicknesses were thinner in patients with epilepsy (N=40, 8-16 years of age) who were receiving valproic acid monotherapy compared with healthy children (Dereci S et al, 2015). The authors concluded that further studies are needed to investigate whether these findings are the result of epilepsy or can be attributed to VPA and whether there are adverse effects of VPA later in life.

In the latest VPA PSUR (covering the period 24 January 2015 - 23 January 2018) the signal retinitis pigmentosa, visual field defect and reduced visual acuity were addressed. It was concluded that the reviewed data were inconclusive to propose product information changes, however the signal should be discussed in next PSUR.
At time of next PSUR, the brand leader MAH should submit a cumulative review of ocular anomalies observed in children after in utero valproate exposure and in particular address the following: retinal fold, retinal rosette/retinal coloboma, coloboma, and myopia. Available data from non-clinical and clinical studies, post-marketing safety databases including Eudravigilance, epidemiological studies and literature should be reviewed and discussed. A discussion should also be provided on plausible underlying

mechanism(s). Based on the information available at that time the MAH should consider amending SmPC section 4.6.

Clinical
89 cases out of which 63 refer to ADRs after transplacental exposure.
Other ADRs mentioned through exposure other than transplacental: Diplopia (N=5), Blepharitis (N=2), Scleral discoloration (N=2), Cataract (N=2) and one case each of the following: Eye colour change, mydriasis, eye disorder due to accidental exposure to product, eye movement disorder/confusional state: drug interaction, Bilateral eye swelling, Multiorgan failure including periorbital oedema, Left retinal vein thrombosis, Periorbital Rash/photophobia, Maculopathy, Miosis, Oculogyric crisis. Optic atrophy.
Diplopia is mentioned in the SmPC.
For the remaining ocular ADR reports, although causality with the use of valproate cannot be excluded, the number of cases is low, case information is incomplete in many and there are a number of confounders such as underlying or intercurrent illness and use of concomitant medications. There is also no reported positive dechallenge and/or rechallenge for the above ADRs with the exception of one case.

In absence of specific MedDRA terms for retinal dysplasia and retinal rosette, MAH's safety database was searched for cases reporting corresponding MedDRA terms: Retinal fold" (PT Chorioretinal folds), "Retinal disorder", "Retinogram abnormal", "Retinal tear", "Retinal scar" or any PT involving "retina%" which may result from a retinal lesion. Narratives of paediatric patients were also search for terms involving: "retina%", "rosette", "dysplasia", or "retinal fold".

Subsequently 3 cases were identified reporting different single events:
- The first patient (4 years old) had an abnormal electroretinogram after 6.5 months of valproate use while using several other medications.
- The second patient (16 years old) experienced retinal shrinkage after use of valproate since childhood, but further detailed information was lacking which hampered the causality assessment.
- For the last patient (9 years old), time to onset of the event of left retinal vein thrombosis was not specified. The patient slowly recovered, but it was not indicated whether recovering of the patient took place after valproate discontinuation or not.
- It is noted that the wording of "retinal fold", "retinal rosette" or "retinal dysplasia" was not found in any cases' narrative of children treated with valproate. The identified cases reported 3 different events.

No relevant information about eye disorders as adverse events was identified in the textbook of Martindale. The MAH also indicated that no such information was found in textbook of Meyler's Side Effects of Drugs and scientific literature. Besides diplopia with rare frequency under Eye disorders, no other event is currently listed under this MedDRA SOC in the SmPC section 4.8.

Regarding retinal dysplasia and retinal rosette, the number of relevant post-marketing cases (up to 31 March 2019) was limited and no pattern of events was identified. Also no other relevant safety information was identified in available literature. The Rapporteur concludes, that based on the identified post-marketing cases a relationship between use of valproate in the paediatric population and occurrence of retinal dysplasia and retinal rosette could not be established.

However, At time of next PSUR, the brand leader MAH should submit a cumulative review of ocular anomalies observed in children after in utero valproate exposure and in particular address the following: retinal fold, retinal rosette/retinal coloboma, coloboma, and myopia. Available data from non-clinical and clinical studies, post-marketing safety databases including Eudravigilance, epidemiological studies and literature should be reviewed and discussed. A discussion should also be provided on plausible underlying mechanism(s). Based on the information available at that time the MAH should consider amending SmPC section 4.6.

- Effects on reproductive system and breast disorders

Non-clinical
In the juvenile animal studies submitted, testes were a target organ. The relative risk associated with exposure of the immature testes compared to that of adult testicular tissue, that has already completed its

sexual maturation, is unknown as are the implications of these findings for the fertility of individuals exposed during infancy.
The SmPC mentions the following adverse effects from the reproductive system and breast disorders: dysmenorrhea, amenorrhea, male infertility, polycystic ovaries, gynaecomastia. Under endocrine system disorders also hyperandrogenism is mentioned.
A study in pubertal girls with epilepsy receiving VPA monotherapy showed that they were more likely to develop signs of hyperandrogenism compared to those on levetiracetam or controls (Rauchenzauner M et al, 2014). The influence of levetiracetam and VPA monotherapy on sex-steroid hormone profile was investigated in another study of 30 prepubertal children (boys and girls) (Rauchenzauer M et al, 2010). VPA-treated children showed greatest androstenedione concentrations when compared to LEV treated children ($p=0.016$) and to controls ($p=0.011$). Finally, in another small study, serum androgen levels and testicular structure was compared in male subjects with epilepsy on monotherapy with carbamazepine, lamotrigine, oxcarbazepine and VPA and healthy controls (Mikkonen K et al, 2004). The patients taking VPA had high serum androstenedione levels at all pubertal stages. The mean testicular volumes did not differ between the patients and the controls. The authors concluded that the long-term health consequences of these reproductive endocrine changes during pubertal development remain to be established.
The reproductive endocrine effects of VPA have not been widely studied in children and it is unclear whether specific monitoring should be implemented to detect any adverse effects early.
The MAHs should continue monitoring ADRs in children from this system, especially regarding long term effects of paediatric exposures on the fertility of males later in adulthood and update the SmPC with relevant clinical data if required.

However, the MAH should re-evaluate possible increased susceptibility of juvenile animals regarding reduced testicular size, taking into account published literature on this subject and findings observed in adult animals. Specifically, when available, kinetics data should be used to determine if juvenile animals may be more susceptible to effects on the testis. As such a re-evaluation is not possible within the time-frame of this procedure, the MAH should perform this re-evaluation in the following PSUR for valproate.

Clinical
36 out of which 7 refer to ADRs after transplacental exposure. The remaining cases involved: amenorrhea (N=12), gynaecomastia (N=8), 3 cases of breast enlargement in female children but no further details are provided, and one case each for the following: vulvar disorder, priapism, vaginal haemorrhage, scrotal/penile swelling, menorrhagia, polycystic ovaries.
Dysmenorrhea, amenorrhea, male infertility, polycystic ovaries and gynaecomastia are mentioned in section 4.8 of the SmPC under Reproductive system and breast disorders.
For the 3 cases of breast enlargement no further details are provided. For the other ADRs presenting with one case and not mentioned in the SmPC, there was insufficient information to assess causality. No new safety signals were identified under this SOC.

No new significant safety information was found through a search in MAH's pharmacovigilance database and in literature regarding "Decreased weight of testis/testes", or related disorders as "testis/testicular atrophy or hypotrophy" in male children with valproate. No update of the SmPC is therefore warranted regarding male reproductive disorders in adolescents. The issue of male infertility with valproate use in the adult population is, however, sufficiently addressed in the SmPC.

Based on the provided literature plausible subclinical effects on reproductive hormones and/or testes/sperm that may start in childhood/puberty and manifest as infertility in adults can be found. Based on the post-marketing data assessed within current procedure, the opinion remains that the requested discussion in next PSUR can be awaited for. The need to study early effects on the male reproductive system and implementation of relevant risk minimisation measures should be taken into consideration by the MAH at that time.

- Blood and lymphatic system disorders

Non-clinical
The MAH argues that blood disorders and lymphoid tissue changes observed in neonatal and juvenile rats at 240 mg/kg/day were also observed in young adult rats. These effects seemed to be more severe in the neonatal and juvenile animals compared to (young) adult, as with the majority of the other adverse effects

observed at the 240 mg/kg/day dose in. In addition, the MAH argues that based on a review by Everds et al. (2013), the changes observed regarding blood disorders and lymphoid tissue changes may be induced by stress secondary to the other observed adverse effects. Based on similar findings in adult compared to juvenile animals and the fact that wording on blood and lymphatic system disorders are mentioned in section 4.8 of the SmPC, changes to SmPC section 5.3 are not needed.

Clinical
122 cases, out of which 3 cases after transplacental exposure. The remaining ADRs were identified: thrombocytopenia (N=58), coagulopathy (N=6), anaemia (N=10), leukopenia/granulocytopenia/neutropenia (N=15), bone marrow failure/pancytopenia/bicytopenia (N=19), macrocytosis (N=2).
The above are well-known adverse drug reactions to VPA and are listed under Blood and lymphatic system disorders in section 4.8 of the SmPC.
6 cases with disseminated intravascular coagulation were identified. In 5 of them other reasons apart from VPA treatment are likely to account for this ADR, such as septic shock, multiorgan failure, other suspect drug, toxic shock syndrome. The SmPC also mentions in section 4.8: coagulation factors decreased, abnormal coagulation tests.

Several adverse reactions are already included in the SOC Blood and lymphatic system disorders (e.g. “Pancytopenia”, “Leukopenia”, “Agranulocytosis”, “Anaemia”, “Thrombocytopenia”, “Bone marrow failure” and/or “Pure red aplasia”). In MAH’s global pharmacovigilance database (up to 31 March 2019), no paediatric cases were identified reporting the PTs terms “Thymus hypoplasia”, “Spleen atrophy” or “Lymphoid tissue hypoplasia”. From literature, also no relevant publication was retrieved about decreased haematopoiesis in children treated with valproate. Therefore, no update of the adverse reactions under the MedDRA SOC Blood and lymphatic system disorders in SmPC section 4.8 is considered necessary.

- Next PSUR

The MAHs are kindly reminded that the signal of retinitis pigmentosa should be discussed in the next PSUR.
In addition, in last PSUSA procedure (PSUSA/00003090/201801) the risk of ‘Impaired growth in children’ has been discussed based on literature and published cases. The issue of impaired growth should be addressed in the next PSUR and if appropriate a proposal to update the SmPC/PL should be provided by the MAH. Based on the assessment of the additional data submitted by the MAH, during current paediatric work-sharing variation, this request for next PSUR remains valid, but the term “impaired grow” should be refined to physical growth and sexual maturation.

SmPC paediatric safety information
It is noted that paediatric information under section 4.8 of the SmPC is provided together with information for adults under different SOCs. For hepatotoxicity, a particularly major safety concern in children, minimal information is provided in section 4.8 and there is cross reference to section 4.4 where extensive information exists. For some psychiatric effects, higher frequency in children is also mentioned.
According to the EC Guideline on Summary of Product Characteristics (SmPC) (2009) and in order to improve the information available on the use of VPA in children, the MAHs were asked to add a separate section under the subheading “paediatric population” in section 4.8. This subsection could clarify the extent and age characteristics of the safety database in children and highlight differences in the safety profile between adults and children, such as the vulnerability of young children to liver injury, as well as psychiatric disorders, such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder which are mentioned in the SmPC to be principally observed in the paediatric population. If effects from other systems are also observed more frequently in children, this should be clarified.

Therefore, the following text was approved for SmPC section 4.8:
Paediatric population
“The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric

disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population."

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

V.1 Overall conclusion

Valproate is a broad-spectrum antiepileptic drug used in children. Based on the submitted paediatric efficacy data it is concluded that no changes are needed in the approved paediatric indications.
The risk of malformations and developmental problems in children exposed to valproate *in utero* was the subject of two Article 31 European referrals. Following the finalisation of the second review, the benefit: risk ratio for valproate for female patients in the treatment of epilepsy and bipolar disorder has changed as VPA is now:

- contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative treatment.
- contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled.

The safety profile of VPA is considered known due to its long-established use in paediatric patients, however potential new safety issues must still be reported and investigated as part of the planned PSURs.
With regard to the paediatric information in section 4.8 of the SmPC, MAH's proposal can be approved, provided hallucinations is omitted as this is not sufficiently justified by the MAH.
Finally, the MAHs should amend the paediatric specific PK information in section 5.2 of the SmPC.
The MAHs are further requested to include details on several signals in the next PSUR.

V.2 Recommendation

The Rapporteur recommends the following changes to SmPC and PIL:

For products licensed for paediatric use:

- SmPC, section 4.8

Paediatric population
"The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population."

- SmPC, section 5.2

"Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months showed considerable variability ranging from 1 to 67 hours. In children aged 2-10 years, valproate clearance is 50% higher than in adults."

- PL, section 4

"Additional side effects in children
Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, infection of the pancreas (pancreatitis), aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder."

For products not licensed for paediatric use:

- SmPC, section 4.8

Paediatric population
"The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver

damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population."

- PL, section 4

"Additional side effects in children
Some side effects of valproate occur more frequently in children or are more severe compared to adults. These include liver damage, infection of the pancreas (pancreatitis), aggression, agitation, disturbance in attention, abnormal behaviour, hyperactivity and learning disorder."

- If appropriate, the following paragraph in section 4.2 should be amended as follows:

Paediatric population
"The efficacy ~~**and safety**~~ of [Product name] in children below 18 years of age <in the treatment of manic episodes of bipolar disorder> has not been established. **With respect to safety information in children see section 4.8.**"

For further follow-up (as part of other regulatory procedures):
Non-clinical

- The brand leader MAH should re-evaluate possible increased susceptibility of juvenile animals regarding reduced testicular size, taking into account published literature on this subject, including the literature referenced by the CMS UK and findings observed in adult animals. Specifically, when available, kinetics data should be used to determine if juvenile animals may be more susceptible to effects on the testis. The MAH should perform this re-evaluation and discuss the relevance of the results for humans in the following PSUR for valproate.
- The brand leader MAH is asked to further discuss the dilated renal tubules findings in the context of the available non-clinical literature and in-house data of valproate findings in the kidney during pregnancy for juvenile animals and in adult animals, preferably also taking into account available kinetics data. Subsequently, the MAH should discuss the relevance of the dilated renal medullary tubules finding in the PND4-PND18 study for exposure during human embryonic development and treatment of premature-born neonates. The MAH should perform this evaluation in the coming PSUR of valproate.

Clinical

- The MAHs are kindly reminded that the signal of retinitis pigmentosa should be discussed in the next PSUR.
- In the last PSUSA procedure (PSUSA/00003090/201801) for valproate containing product the risk of 'Impaired growth in children' has been discussed based on literature and published cases. It was concluded that the issue of impaired growth should be addressed in the next PSUR and if appropriate a proposal to update the SmPC/PL should be provided by the MAHs. Based on the Rapporteur's assessment of the additional data submitted by the MAHs, during current paediatric work-sharing variation, this request for next PSUR remains valid, but the term "impaired growth" should be refined to "physical growth" and "sexual maturation" in children treated with valproate.
- The brand leader MAH should submit a cumulative review of ocular anomalies observed in children after *in utero* valproate exposure and in particular address the following: retinal fold, retinal rosette/retinal coloboma, coloboma, and myopia. Available data from non-clinical and clinical studies, post-marketing safety databases including Eudravigilance, epidemiological studies and literature should be reviewed and discussed. A discussion should also be provided on plausible underlying mechanism(s). Based on the information available at that time the MAH should consider amending SmPC section 4.6.

Not all member states endorsed the Rapporteur's recommendation at the end of the Worksharing procedure:
- UK considered that the updates to SmPC sections 4.8 and 5.3 should be more extensive than proposed by the Rapporteur. Additionally, UK considered that the effects of valproate on the risk of male reproductive disorders should be further investigated by the MAH, and not only addressed in the upcoming PSUR as recommended by the Rapporteur.