Proposal for changes to Sodium Valproate on the Model Lists of Essential Medicines and Essential Medicines for Children

Review of Sodium Valproate prescribed to women of child bearing potential
For the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines List for Children (EMLc)

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1. Summary statement of the proposal for inclusion, change or deletion.

This proposal was produced following the Independent Medicines and Medical Devices Safety Review (IMMDS) in the UK and the report which was released on 9th July 2020 (1) .

Based on currently available evidence we suggest the WHO consider potential harm caused by the use of Sodium Valproate, and other anti-convulsant medications during pregnancy, and that the medication Sodium Valproate has vital changes made to the warnings of the drug on the essential medicines list for adults and paediatrics (EML & EMLc) Noting :

- Sodium Valproates teratogenic effects on the fetus causing birth defects (Spina Bifida, Kidney & Heart malformations, cleft lip & palate, neurodevelopmental problems such as Autistic spectrum disorders.
- The failure of changes to prescribing in European countries following instruction from the European Medicines Agency
- Sodium Valproate's effects on the sperm
- Animal studies suggesting possible transgenerational effects on the next generation of offspring of those affected by Sodium Valproate (2).

There is a substantial body of evidence on the efficacy and the danger of Valproate when prescribed to women and girls of child bearing potential. The library of evidence supplied through research into Sodium Valproate taken by women has been available since the late 1970's, with the possibility of a syndrome questioned in 1987 and the definite diagnosis of the Fetal Valproate Syndrome made in 1995.

Most evidence was available through the Summary of Product Characteristics and the Data sheets previously available to clinicians but not made available to female patients, with many studies on the topic and their substantial findings made throughout the 1980's onwards.

The prospective NEAD study, completed by the UK and United States of America, over a 6-year period showed the damages caused by Sodium Valproate in pregnancy, and that Valproate above any other Anticonvulsant drug cognitive problems to those exposed (3).

Following on from that study, in 2013 the publication of another vital study completed by UK researchers (4) showed that 40% of those exposed to Valproate in utero would have neurodevelopmental problems, Autistic Spectrum disorders, speech and language problems and memory difficulties.

The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and the European Medicines Agency (EMA) became involved through work of the Independent Fetal Anticonvulsant Trust (INFACT) and in the following 3 years worked to introduce updated warnings to the women prescribed Sodium Valproate in their children bearing years. In April 2018, in the UK this was upgraded to a mandatory action and a Pregnancy Prevention Programme was introduced to avoid prescribing to those who were of child bearing potential and could use other anticonvulsant drugs.

According to the MHRA in the UK the numbers of those women prescribed Valproate in their child bearing years slowly declined, however the figures of those children affected by Valproate in pregnancy did not, with 400 babies affected in any one year during this time (5).

The Independent Fetal Anticonvulsant Trust (INFACT) continued to survey those prescribed Valproate, finding that 85% of those who took the survey had failed to have a discussion with their doctor about changing their medication and that 55% had never had the Pregnancy Prevention Programme discussed with them by their prescribing doctor.

Safety of a medication is paramount, especially when being used in pregnancy. The drug company producing the majority of sodium Valproate have been aware of its teratogenic properties since licensing began yet governments worldwide continue to allow the drug to be prescribed to this group of patients due to its presence and the particular language used on the Essential Medicines List.

Therefore, taking into account the damage caused in pregnancy, the vast amount of research and evidence on Valproate in pregnancy and the ignorance still towards these dangers, we propose that Valproate:

- Should have an additional Cautionary Note attached to its listing in the EML and EMLc
- Valproate should be transferred to the Complementary Listing
- Valproate should receive additional monitoring with a view to the De-prescribing in the UK
- Extra guidance given to Valproate and off label prescribing.

It is essential that countries are aware of the dangers of prescribing Valproate in pregnancy, and for those women whose children are exposed to be informed of the damage it can cause. Therefore, it is vital that all countries introduce a similar Pregnancy Prevention Programme to that of the UK for Valproate and the WHO support this by introducing the changes proposed above.

2. Relevant WHO technical department and focal point (if applicable).

WHO Department of Mental Health and Substance Use, Dr Tarun Dua

3. Name of organization(s) consulted and/or supporting the application.
N/A

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Valproic acid
N03AG01

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Valproic acid (sodium valproate) is currently included on the core list of the EML and EMLc in the following dose forms:

Oral liquid: 200 mg/5 mL
Tablet (crushable): 100 mg
Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate)

Valproic acid (sodium valproate) is currently included on the complementary list of the EML and EMLc in the following dose forms:

Injection: 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

The application applies to the current listings of valproic acid (sodium valproate) as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Sodium Valproate is a drug used worldwide from a number of conditions, and continues to undergo clinical trials for its use in other illnesses and disease such as cancer, fibromyalgia, chronic pain, autism and impulsive control disorders, many of which apply to women of child bearing age where the woman is able to become pregnant.

Valproate has continuous use also as an off-label drug with many specialists prescribing it and the where the regulators are not made aware of the condition it is being used for, this also include private prescriptions.

Valproate in comparison to other AED's is the most potent to use during pregnancy, with research showing that other AEDs such as Carbamazepine, Lamotrigine and Levetiracetam has a lesser effect on baby. However, due to the lack of research on other AEDs in pregnancy, especially the newer ones, we would still air caution when prescribing without giving an informed choice or warnings of the chances of the effects in pregnancy. INFACT would like to see and advise standard information for women prescribed any anticonvulsant drug during her child bearing years, and to ensure she has the informed choice to make.

Due to INFACTs work with Sodium Valproate and Governing bodies within the UK, we are aware that around 400 babies are born to Valproate each year, around 10% of those affected will be born with a major malformation such as Spina Bifida, Cleft Lip & Palate., Kidney and heart malformations. However as stated in the 2013 research paper by Bromey et al "***The Prevalence of Neurodevelopmental disorders in Children prenatally exposed to antiepileptic drugs"*** *(4),* we were then aware of 40% of those exposed to Valproate in utero would have Neurodevelopmental disorders such as Autism. In 2018, within the UK the Independent Medicine and Medical Devices Safety Review was launched and came to its conclusions in July 2020 where it was stated that 1 in 2 babies exposed to Valproate would be harmed by it, a stark figure (1).

The WHO mhGAP Intervention Guide (Version 2.0, 2016) includes recommendations for the use of valproate for the treatment of manic episodes in bipolar disorder and epilepsy (6). These are the indications for which valproate is currently included on the WHO Model Lists.

8. Information supporting the public health relevance.

Epilepsy accounts for a significant proportion of the world's disease burden affecting approximately 50 million people worldwide. The point prevalence of active epilepsy (defined by regular treatment with antiseizure medicines, or when the most recent seizure has occurred within the last 5 years) is reported as 5.49 per 1000 persons in high-income countries (95%CI: 4.16-7.26) and 6.68 per 1000 persons in low- and middle-income countries (95% CI: 5.45-8.10) (7, 8).

INFACT calculates that 6.4% of women of child bearing potential in the UKs Epilepsy population are prescribed Valproate, with 400 pregnancies (1.25%) every year.

Mental Health problems i.e.; Bipolar, depression and anxiety are reported to be primary drivers of disability in the UK, with over 40 million aged between 20 and 29 years being affected (9, 10).

As Valproate takes a shorter time to work than Lithium for Bipolar, and may be more effective that Lithium for treating mania or raid cycling bipolar disorder, a UK audit sample was carried out of 6705 patients, 3854 were 50 years or younger, Valproate was prescribed to 24% in this age group (11).

The 2018 research paper "**A UK Clinical Audit addressing the quality of prescribing of Sodium Valproate for Bipolar disorder in Women of child bearing age"** (11) states:

".it is unclear to what extent this reflects clinicians' concerns about teratogenicity or is driven by perceptions of the indications for Valproate."

Valproate as we are aware is 'overused' in the US for Bipolar (12). The drug was approved by the FDA in 1994, but was not licenced for Bipolar, however to date its common prescription use is off-label with many women uninformed of its teratogenicity.

INFACT estimates that in the UK Valproate continues to be prescribed to around 32,000 women, the MHRA report prescriptions given to 18,000 in England and a further 18,000 in Scotland, Northern Ireland and Wales.

At present, there are around 600,000 people in the UK with a known diagnosis of epilepsy (13) with approximately 2,500 births occurring annually to women with Epilepsy prescribed AEDs in the UK.

In the UK 1 in 103 people in every week, over 600 people are given an Epilepsy diagnosis, approx. 139,000 are women. The cost to the UK health service is around £1.5 billion annually (13), however that figure would treble when added in the figure of those affected by Sodium Valproate each year.

With around 32,000 women in the UK at present prescribed Valproate and 400 of those women giving birth every year to babies exposed and affected by the drug, the autistic population continues to rise.

The majority of the families affected by the burden of Valproate constantly attempt to seek ways in which to live a normal life, yet are continuously held back by health issues surrounding the effects of Sodium Valproate. This in turn has a huge effect on the country's economy creating unemployed families due to the child's Fetal Valproate Spectrum Disorders (FVSD), the mothers Epilepsy worsened by the stress of caring for her child, and the father giving up work to care for the family. Most FVSD families live on benefits provided by the country, the health systems which looks after them providing medical and physical health care, the social services to help support them through their crisis. Most parents live in fear of what will happen to their children once they are no longer here to care for them, creating excess stress and worry (14).

In the UK there are around 18,000 families in this situation, with their children of all ages ranging from 0 - 47yrs, who have been affected by the drug since its licensing in 1973.

Valproate has created a ripple effect on the population around the world, with those affected by unable to work, as their parents before them, due to ill health and disabilities caused through FVSD.

Working constantly with the MHRA, Dept of Health and National Institute for Clinical Excellence (NICE) in the UK, INFACT have played a huge part of the updating of recommendations and guidance to clinician of the dangers of Valproate prescribed to women of child bearing potential, taking part in the drawing together the warnings used in the Pregnancy Prevention Programme, however, since the introduction of the PPP in April 2018 the majority of doctors still fail to give women the information booklet, information about other possible AEDs and the signing of the Acknowledgment of Risk form. We believe this will be an ongoing factor within countries who have warnings in place without changes made to Valproate's description on the Essential Medicines List for Adults and Children and the proposed changes made.

With the growing amount of new and most probably better AEDs coming to the market and the low number of women who are unable to use any other drug than Valproate, we feel it would be in the best interest of

prescribers, pharmacists and patients if changes were made to bring the dangers to the attention of those prescribing, dispensing and taking this medication.

Through further research and work with the MHRA we also know that the dose differential bears no impact on the effects of the foetus. There is no lowest dose for Valproate which does not affect the child in utero and so there is no longer believed to be a safe dose regime which is suitable for women of child bearing potential.

A dose-related risk of developmental disorders has been reported for valproate with daily doses above 800 mg to 1000 mg associated with poorer cognitive outcomes in children exposed (15). However, based on the available data, it is not possible to establish a threshold dose below which no risk of developmental disorders exists (5) and this continues to require further research.

9. Review of benefits: summary of evidence of comparative effectiveness.
N/A

10. Review of harms and toxicity: summary of evidence of safety.
Contraindications & Warnings

The licenced drug company from 1973 warned of Valproates teratogenic effects with contraindications added over time, bearing in mind these warnings did not reach the patient but gave heed to the prescribing doctor.

Epilim: When Valproate was first registered, there were no specific contraindications;
September 1974. Data Sheet contained the following information in relation to pregnancy:
"Uses …In women of child bearing age, the product should only be used in severe cases or in those resistant to other treatment."

"CONTRA-INDICATIONS, WARNINGS, ETC
Precautions - women of childbearing age This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings." The current contraindications for Epilim (together with the dates they were added to the Summary of Product Characteristics (SmPC)) are shown below. The current SmPC (revised 23 March 2020) is available at https://www.medicines.org.uk/emc/product/1446/smpc#gref.

This information was stress to the UK Department of Health in the early 1980's by the pharmaceutical company with information for the patient, however the governmental body refused to issue the warnings to the patients.

Date Added	**Contraindication**
1991	Hypersensitivity to Sodium Valproate Active liver disease Personal or family history of severe hepatic disfunction, especially drug related.
1996	Porphyria

2015	Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder
2016	Patients with known urea cycle disorders
2018	In pregnancy unless there are no suitable alternative treatment* In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled

Sodium Valproate is also prescribed under the name of Depakote in the United States and in the UK.

When Depakote was authorized in 2000, the contraindications included in the SmPC reflected those listed for Epilim at that time. All additional contraindications to use of Epilim introduced since that time have also been applied to Depakote. In addition, to the above, following the recent review by the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) (16) the Depakote has also been contraindicated in the following circumstances:

• In pregnancy

• In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled

Date in Compendium	**Information in data sheet**
1974 -76	"Uses In the treatment of generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or in those resistant to other treatment." "Contra-indications, warnings, etc. "Women of child-bearing age: This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings."
1977- 81	"Uses In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment." "Contra-indications, warnings, etc. Women of child-bearing age: Sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals. In women of child-bearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings."
1982-83	"Uses In the treatment of generalised, focal or other epilepsy. In women of child-bearing age, the product should only be used in severe cases or in those resistant to other treatment." Women of child-bearing age: Valproic acid or sodium valproate, like certain other anticonvulsants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazard suggested by these findings."
1984-90	In women of childbearing age, Epilim should be used only in severe cases or in those resistant to other treatment." "Contra-indications, warnings, etc. Women of child-bearing age: Valproic acid or sodium valproate, like certain other anticonvulsants, has been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against

	the possible hazard suggested by these findings and their pregnancies should be carefully monitored".
1989-90	Note: A licence for Epilim intravenous formulation was approved during 1988, and different wording was approved in the pregnancy section compared with the other licenced formulations, The Datasheet compendium entry for Epilim Intravenous in 1989/90 was as follows: Some studies have demonstrated an increase in the expected incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated. There is evidence of teratogenic effects with anticonvulsants including Epilim in animals and there have been reports of congenital abnormalities in offspring of a small number of epileptic patients receiving therapy during pregnancy. In pregnancy, the benefits of these compounds should be weighed against the possible hazard suggested by these findings and their pregnancies should be carefully monitored."
1990-92	(wording now in line for all Epilim formulations) "Women of child-bearing age. An increased with epilepsy both untreated and treated has been demonstrated. There have been reports of foetal anomalies including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%. Such pregnancies should be carefully screened by alphafoetoprotein measurement and ultrasound and if indicated amniocentesis. In all pregnancies monotherapy is to be recommended and the benefits of antiepileptic therapy must be evaluated against the possible risks and the patients should be informed of these and the need for screening". incidence of congenital abnormalities in off-spring born to mothers
1993-94	"Use in Pregnancy and Lactation An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate. The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Pregnancies should be carefully screened by alpha-foetoprotein measurement and ultrasound and if indicated amniocentesis. In all pregnancies monotherapy is to be recommended and dosage reviewed. The benefits of antiepileptic therapy during pregnancy must be evaluated against the possible risks and patients should be informed of these and the need for screening."
1994-97	"Use in Pregnancy and Lactation An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate. The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate".
1998-99	Uses in Pregnancy and Lactation: (- changes highlighted in text) An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate. The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1 to 2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving

	anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child-bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound, and other techniques if appropriate".

Throughout the 1970's from first licencing to the late 1990's the drug company continuously reported for the medical profession, through the Summary of Product Characteristics the findings and dangers when prescribing to pregnancy women, however it wasn't until the mid 1990's that the drug issued its first Patient Information leaflet which noted to female patients "If pregnant please consult your doctor", yet UK doctors were not forthcoming with the information due to lack of instruction from the Medicines and Healthcare Products Regulatory Agency (MHRA)

This attitude has continued through to the present day, even though from 2010 onwards the information in the SmPCs have been more damning

2010	Section 4.4 Special warnings: Women of childbearing potential (see section 4.6): A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child. This decision is to be taken; before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy (see also section 4.6 Pregnancy and Lactation). Precautions: Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation). Section 4.6 Women of childbearing potential should not be started on Epilim without specialist neurological advice. Section 4.4 Special warnings: Women of childbearing potential (see section 4.6): A decision to use Epilim in women of childbearing potential should not be taken without specialist neurological advice, and only if the benefits of its use outweigh the potential risks of congenital anomalies to the unborn child. This decision is to be taken; before Epilim is prescribed for the first time as well as before a woman already treated with valproic acid is planning pregnancy. Adequate counselling should be made available to all women of childbearing potential regarding the risks associated with pregnancy (see also section 4.6 Pregnancy and Lactation). Precautions: Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation). Section 4.6 Women of childbearing potential should not be started on Epilim without specialist neurological advice. involving various body systems in offspring born to mothers with epilepsy treated with valproate. The data suggest that the use of valproate is associated with a greater risk of certain types of these malformations (in particular neural tube defects) than some other anti-epileptic drugs. Both valproate monotherapy and valproate as part of polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including sodium valproate is associated with a higher risk of abnormal pregnancy outcome than sodium valproate monotherapy. Data have suggested an association between in-utero

	exposure to valproate and the risk of developmental delay (frequently associated with dysmorphic features), particularly of verbal IQ. However, the interpretation of the observed findings in offspring born to mothers with epilepsy treated with sodium valproate remains uncertain, in the view of possible confounding factors such as low maternal IQ, genetic, social, environmental factors and poor maternal seizure control during pregnancy. Autism spectrum disorders have also been reported in children exposed to valproate in utero. - In view of the above data When a woman is planning pregnancy, this provides an opportunity to review the need for anti-epileptic treatment. Women of child-bearing potential should be informed of the risks and benefits of the use of Epilim during pregnancy. Specialist advice is required and physicians are strongly encouraged to discuss reproductive issues with their patients before Epilim is prescribed for the first time or a woman already treated with Epilim is planning a pregnancy. Folate supplementation, prior to pregnancy, has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. Although no direct evidence exists of such effects in women receiving anti-epileptic drugs, women should be advised to start taking folic acid supplementation (5mg) as soon as contraception is discontinued. The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses, as abnormal pregnancy outcome tends to be associated with higher total daily dosage and with the size of an individual dose. The incidence of neural tube defects rises with increasing dosage, particularly above 1000mg daily. The administration in several divided doses over the day and the use of a prolonged release formulation is preferable in order to avoid high peak plasma levels. During pregnancy, Epilim anti-epileptic treatment should not be discontinued without reassessment of the benefit/risk. Nevertheless, specialised prenatal monitoring should be instituted in order to detect the possible occurrence of a neural tube defect or any other malformation. Pregnancies should be carefully screened by ultrasound, and other techniques if appropriate (see Section 4.4 Special Warnings and Precautions for use). - Risk in the neonate Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken Epilim during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and other anti-epileptic enzyme inducing drugs. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
2015	As a result of the PRAC review the information in the SmPC was updated and all relevant warning text related to pregnancy is re-produce below. Section 4.2 Posology and method of administration Female children, female adolescents, women of childbearing potential and pregnant women Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses. Section 4.4.1. Special Warnings Female children/Female adolescents/Women of childbearing potential/ Pregnancy: Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero

	to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Epilim plans a pregnancy or if she becomes pregnant. As a result of the PRAC review the information in the SmPC was updated and all relevant warning text related to pregnancy is re-produce below. Section 4.2 Posology and method of administration Female children, female adolescents, women of childbearing potential and pregnant women Epilim should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably Epilim should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses. Section 4.4.1. **Special Warnings Female children/Female adolescents/Women of childbearing potential/ Pregnancy:** Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with Epilim plans a pregnancy or if she becomes pregnant. Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of Epilim during pregnancy (see section 4.6). The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks. In particular the prescriber must ensure the patient understands: • The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders . • The need to use effective contraception. • The need for regular review of treatment. • The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6). Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy Section 4.4.2 Precautions Pregnancy: Women of childbearing potential should not be started on Epilim without specialist neurological advice. Adequate counselling should be made available to all pregnant women with epilepsy of childbearing

	potential regarding the risks associated with pregnancy because of the potential teratogenic risk to the foetus (see also section 4.6 Pregnancy and Lactation). **Section 4.6. Fertility, pregnancy and lactation** Epilim should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible**.** **Pregnancy Exposure Risk related to valproate** Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. Congenital malformations Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 - 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. Developmental disorders Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long-term outcomes.

	Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). Female children, female adolescents and woman of childbearing potential (see above and section 4.4) If a Woman wants to plan a Pregnancy • During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. • In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed • In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to: - Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations to avoid high peak plasma concentrations. - Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. - To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations. Risk in the neonate - Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers.

	Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates. - Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy. - Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy. - Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy. Breastfeeding Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8) A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Epilim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Fertility Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation. **Section 4.8. Undesirable Effects** Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

2018	As a result of the PRAC review the information in the SmPCs was updated and all relevant warning text related to pregnancy is re-produced below. **4.2 Posology and method of administration** Female children and women of childbearing potential Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6). Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4). Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if

	possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6). 4.3 Contraindications Depakote is contraindicated in the following situations: • In pregnancy (see sections 4.4 and 4.6) • In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6). 4.4 Special warnings and precautions for use 4.4.1 Special warnings Female children, women of childbearing potential and pregnant women: **Pregnancy Prevention Programme** Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6). Depakote is contraindicated in the following situations: • In pregnancy (see sections 4.4 and 4.6) • In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6). Conditions of Pregnancy Prevention Programme: The prescriber must ensure that: • Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks. • The potential for pregnancy is assessed for all female patients. • The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero. • The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed. • The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.

	• The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of bipolar disorder. • The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued. • The patient understands the need to urgently consult her physician in case of pregnancy. • The patient has received the Patient Guide • The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form). These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. Female children The prescriber must ensure that: • The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche. • The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate in utero. In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood **Pregnancy test** Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing

	potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy Contraception Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception. **Annual treatment reviews by a specialist** The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content. **Pregnancy planning** If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued. **In case of pregnancy** If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6). **Pharmacists must ensure that:** • The Patient Card is provided with every valproate dispensation and that patients understand its content. • Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy. Educational materials in order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate

	An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist. Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of bipolar disorder. **4.6 Fertility, pregnancy and lactation** • Valproate is contraindicated as treatment for bipolar disorder during pregnancy • Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4). **Pregnancy exposure risk related to valproate** Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. **Teratogenicity and developmental effects** Congenital malformations Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. Developmental disorders Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these

	effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to valproate show that up to 30 – 40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long-term outcomes. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). **Female children and woman of childbearing potential (see above and section 4.4)** If a woman plans a pregnancy If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an alternative treatment prior to conception and before contraception is discontinued. Pregnant women Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. All patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies. However, the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. Risk in the neonate

	• Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates. • Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy . • Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy. • Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Throughout all the relevant and constant changes to the SmPC and a change in legislation to equipped clinicians and doctors with the evidence required to give patients, women continue to fail to receive it due to governmental changes to legislations such as the Quality Outcomes Framework (QOF) and the Statement of Financial Entitlements.

The Pregnancy Prevention Programme, after almost a 3-year life span in the UK and with ongoing discussions in other countries such as France, Belgium, New Zealand etc. Valproate continues to be prescribed with no contraindications or warnings relayed to the female patients.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.
N/A

12. Summary of regulatory status and market availability of the medicine.
Sodium valproate has wide global regulatory approval and market availability.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).
Reference standards exist for valproate in the British, United States, European and International Pharmacopoeias.

References

1. The Independent Medicines and Medical Devices Safety Review. First Do No Harm – The report of the Independent Medicines and Medical Devices Safety Review. Available from https://www.immdsreview.org.uk/Report.html. Accessed 25 November 2020. 2020.

2. Choi CS, Gonzales EL, Kim KC, Yang SM, Kim JW, Mabunga DF, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. Sci Rep. 2016;6:36250.
3. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244-52.
4. Bromley RL, Mawer GE, Briggs M, Cheyne C, Clayton-Smith J, García-Fiñana M, et al. The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. J Neurol Neurosurg Psychiatry. 2013;84(6):637-43.
5. Medicines and Healthcare products Regulatory Agency. Medicines related to valproate: risk of abnormal pregnancy outcomes. Drug Safety Update volume 8 issue 6 January 2015: 1. Available from https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes. Accessed 25 November 2020.
6. World Health Organization. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP) – version 2.0. Geneva: World Health Organization; 2016.
7. World Health Organization. Epilepsy: a public health imperative. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
8. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017;88(3):296-303.
9. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743-800.
10. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095-128.
11. Paton C, Cookson J, Ferrier IN, Bhatti S, Fagan E, Barnes TRE. A UK clinical audit addressing the quality of prescribing of sodium valproate for bipolar disorder in women of childbearing age. BMJ open. 2018;8(4):e020450.
12. Osser DN. Valproic Acid: Overused in Bipolar Disorder? The Psychiatric Times. Volume 37, Issue 7. July 28 2020. Available from https://www.psychiatrictimes.com/view/valproic-acid-its-role-in-bipolar-disorder. Accessed 25 November 2020.
13. Epilepsy Research UK. Epilepsy Statistics. Available from https://epilepsyresearch.org.uk/about-epilepsy/epilepsy-statistics/. Accessed 25. November 2020.
14. Morley K. Reducing risks for pregnant women with epilepsy: A qualitative study exploring experiences of using a toolkit at the antenatal booking appointment. Epilepsy Behav. 2020;103(Pt B):106418.
15. Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014;2014(10):Cd010236.
16. European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy. 9 February 2018. Available from https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy. Accessed 25 November 2020 [press release].