**VALPROATE, GENERALISED EPILEPSY AND WOMEN OF CHILDBEARING POTENTIAL**

Valproate is a highly effective anti-epileptic drug that has been used for almost 50 years. Valproate taken in pregnancy has a higher risk of causing abnormalities to the unborn child, compared with other anti-epileptic drugs.

A widely held view is that valproate should not be used in any girls or women who could become pregnant, unless other anti-epileptic drugs have failed. A problem is that for some people with epilepsy, other anti-epileptic drugs may not be as effective as valproate.

This brochure will explain the risks of using and not using valproate to both the baby and the mother.

**AVOIDING PREGNANCY WHILST ON VALPROATE**

Highly effective contraception is required to reliably avoid pregnancy. Valproate does not affect the efficacy of the contraceptive pill. The oral contraceptive pill (at normal doses) does not interact with valproate, however, it must be taken daily to ensure effectiveness. Barrier methods (condoms, diaphragms) may also fail to prevent pregnancy. More reliable methods include levonorgestrel intrauterine device (Mirena) or progestogen-only implant (Implanon) and 3-monthly injections (Depo Provera), which have the advantage of the user not having to remember to take medications.

**ANTI-EPILEPTIC DRUGS and PREGNANCY**

* Most of the information has come from large Pregnancy Registers around the world. We have the **Australian Pregnancy Register for Women on Anti-Epileptic Drugs (APR)** which has been monitoring women taking anti-epileptic drugs during their pregnancies for 20 years**.** **TEL 1800 069 722**
* Anti-epileptic drugs as a group carry a two- to three-fold increased risk of causing birth defects, but the risks vary substantially across different anti-epileptic drugs. In fact, with some anti-epileptic drugs the risk of birth defects does not differ substantially from the risk seen in women who do not take any medicines. Valproate has the highest malformation risk which is dose-dependent (the higher the dose, the higher the risk)
* The least risk has been shown with levetiracetam (Keppra) and lamotrigine (Lamictal).

**VALPROATE RISKS TO THE UNBORN CHILD**

1. **STRUCTURAL ABNORMALITIES**
	* The most common abnormalities in babies whose mothers took valproate involve the heart, penis, kidneys, or extra fingers or toes. The most serious is spina bifida, where the spine does not develop normally and in severe cases, the child will be unable to walk or control their bladder. Some of these malformations can be helped by surgery.
	* There is a dose-dependent risk of structural malformation.
		1. Valproate doses of 1500 mg per day or more, has a risk as high as 25% (1 baby out 4 being affected).
		2. Valproate at doses between 700 to 1450 mg/day, has a risk of approximately 10%. (10 babies in 100 affected, 90 babies in 100 will not be affected).
		3. Valproate doses of 650 mg or less per day, has a risk of approximately 6.3% (6 babies in 100 affected).
		4. There appear to be a lower risk at valproate doses of 500 mg or less per day (possibly lower than 5%).
	* The dose of valproate in the first trimester (12 weeks) is the most critical as this is the time abnormalities may occur when organs are being formed.
2. **INTELLIGENCE**
	* Lower intelligence has been found in children whose mothers took 800mg or more of valproate while pregnant.
	* The risk for an adverse effect on intelligence is dose-dependent.
	* It is not known exactly when during pregnancy that this effect occurs. This means that valproate should be avoided or, if essential, then the dose should be kept as low as possible throughout pregnancy.
3. **REPORTS OF INCREASE IN AUTISM SPECTRUM DISORDERS**
	* There may be a four-fold increase in autism spectrum disorders in children whose mothers took valproate during pregnancy.
	* This risk was found with both low and high doses of valproate.
	* It is not known exactly when during pregnancy that this effect occurs. This means that valproate should be avoided or, if essential, then the dose should be kept as low as possible throughout pregnancy.
	* If there is a family history of autism spectrum disorders, there a higher risk, even without valproate.

**EPILEPSIES AND ANTI-EPILEPTIC DRUG CHOICE**

1. **Focal epilepsy:**
* There are many anti-epileptic drugs which may be as effective as valproate for focal epilepsy. Thus, valproate should be avoided in the treatment of focal epilepsies in women as there are many other drugs to use, some of which carry lower risks when used in pregnancy.

 **b) Generalised epilepsy**

* Generalised epilepsies often do not respond to many of the anti-epileptic drugs used for focal epilepsies. Valproate is the most effective anti-epileptic drug for this group.
* In women of childbearing potential with generalised epilepsy, the safest effective anti-epileptic drugs for the baby are levetiracetam and lamotrigine.
* While it is ideal to avoid valproate in women of child bearing potential, sometimes valproate alone or in combination may be the only way to gain total control of the seizures.
* Valproate works well in combination with lamotrigine for patients with generalised epilepsies, and may allow seizure control with a much lower dose of valproate.
* If seizures are not being controlled, it is better, where feasible to increase the dose of the other drug, rather than increase the dose of valproate
* There is strong evidence that a low dose of valproate (ideally around 200mg/day) in combination with lamotrigine or levetiracetam, has a lower risk for structural abnormalities and decreased intelligence, compared to a higher dose of valproate on its own.

**REDUCTION OF VALPROATE WHEN PLANNING A PREGNANCY: IS IT SAFE?**

* If a woman with a generalised epilepsy syndrome is already on valproate and then wants to become pregnant (or becomes unexpectedly pregnant), what needs to be done?
	+ **Review the patient for the following:**
		- Is there a need for continuing anti-epileptic drug therapy?
		- Is valproate essential? Can it be reduced or substituted with another anti-epileptic drug?
		- Have other possibly effective anti-epileptic drugs been properly trialled?
		- If valproate is essential and needs to be continued, then is the valproate dose as low as possible?
		- Any dose change needs to be done very carefully and under medical supervision, with the patient understanding that a “breakthrough” seizure could occur which can carry health risks (see below). There is no universally ‘correct’ dose, and it is not possible to know what the lowest effective dose for each person will be in advance. The dose, however, required to prevent seizures may be reasonably consistent in each person, so information gained in one pregnancy is likely to be helpful in the next.
		- Ideally, any change in treatment should be completed at least 3 months before conception, so there is time to see if the epilepsy is controlled.
	+ **If medication is changed or reduced:**
		- The patient should be counselled about the risk of recurrent seizures.
		- Driving needs to be ceased for at least 3 months. This can be reviewed if seizures are controlled on a lower dose. (See Assessing Fitness to Drive Guidelines)
		- There needs to be at least one competent person around as much as possible when medication is changed or reduced, due to the risk of seizures. Ideally, this includes a partner at night in case of seizures while asleep.
* **Reduction in valproate imposes RISKS to both mother and baby**
	+ **Risks to the mother**
* There is a risk of losing seizure control when valproate is reduced or ceased in the context of pregnancy. This has been recently documented in two Pregnancy Registers. About 30% of women who stopped valproate during pregnancy experienced seizures (this is about twice the rate in women who continued valproate).
* There are reports of the occurrence of severe seizures, status epilepticus (frequent unstoppable seizures) and deaths from seizures when anti-epileptic drugs are reduced in planning for pregnancy, or during the pregnancy.
* If generalised convulsive seizures are poorly controlled, there is a risk of sudden unexpected death in epilepsy (SUDEP) (1/1000 patients / year).
	+ **Risks to the baby**
* If seizures are poorly controlled, there is the risk of injury to the foetus, should the mother fall during the seizure.
* Frequent seizures (> 5 generalised convulsive seizures during pregnancy) have been linked to lower intelligence in the offspring in one study.
* It has also been reported that babies whose mothers experienced seizures during pregnancy had an increased risk of low birth weight and premature birth.
* If the mother has very severe seizures with loss of oxygen, there is a risk to the developing baby. Infrequent cases of death of the unborn baby have been reported in Pregnancy Registers.

**PREGNANCY, BIRTH, AFTER THE BIRTH CARE**

* + - Women with epilepsy have a higher risk of complications in pregnancy and birth
		- Good seizure control is highly desirable for the safety of both the mother and child
		- If the dose of valproate has been reduced early in pregnancy, it may need to be increased late in the pregnancy so that seizures do not occur during the birth.
		- Be aware that sleep deprivation after the birth may increase the risk of myoclonic jerks in some women with juvenile myoclonic epilepsy, with the consequent risk of dropping the newborn baby, as well as tonic-clonic seizures. Doses of antiepileptic drugs effective during the pregnancy may be inadequate after the birth
		- Breast feeding is positively encouraged, and the benefits outweigh the risk even for mothers taking valproate. However, breast feeding often causes sleep deprivation.

**PRESCRIBING CHECKLIST FOR VALPROATE**

The following checklist is available to ensure there has been a shared discussion between the patient and the treating neurologist in regard to the risks and benefits of taking valproate during potential child-bearing years.

This information may change over time. Please remember to discuss the subject regularly.

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| **PRESCRIBING CHECKLIST FOR VALPROATE USE IN WOMEN AND GIRLS****(for consumers and prescribers)** | (Affix patient identification label here)URN:Family Name:Given Names:Address:Date of Birth: Sex: [ ]  M [ ]  F [ ]  I |
| **This form is part of a shared decision-making process regarding the use of valproate.****To be discussed and signed by the patient and/or carer and the prescriber.** |
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| **Diagnosis** ……………………………….. …………………………………………………………………………………………. I confirm that the above-named patient needs valproate because she has a generalised form of epilepsy that is not adequately treated by one or more other anti-epileptic drugs. Yes NoPrevious treatments trialled and reasons for discontinuation: ………………………………..…………………………………………………………………………………………………………………………………………………..…………………………………………………………………………………………………………………**Current valproate dose** ……………………………….. ……………………………………………………………………… The reasons for the current dose are:………………………………..…………………………………………………………………………………………………………………………………………………..…………………………………………………………………………………………………………………Was valproate used in combination with lamotrigine or other anti-epileptic drugs? Yes NoIf so, which other drugs were used in combination with valproate ……………………………………….. Are the risks to the mother and child of not being on valproate considered to outweigh the risks to a potential child ?  Yes NoRisks if not on valproate are: ……………………………………………………………………………………………………………………………………………………………………………………………………………………………………………….  |
| **Considerations prior to commencement of valproate** Folic acid supplmentation DiscussedConsideration of pregnancy test DiscussedImportance of adequate contraception discussed DiscussedEffective contraception is essential while taking valproate.Neither condoms nor oral contraceptives alone are sufficient. Long-term contraceptives are strongly recommended.Highly effective contraception is defined as user-independent method (long-acting reversible contraceptives): * copper intrauterine device (Cu-IUD),
* levonorgestrel intrauterine system [Mirena ®]
* progestogen-only implant [Implanon®]
* long-acting progesterone injections (Depo Provera)

If user-independent method is not chosen, two complementary forms of contraception should be consideredConsultation with GP or gynaecologist recommended Discussed  |
| **Summary of risks in children exposed to in-utero valproate**  Discussed 1. Doses above 650mg valproate/day have been shown to increase risks of structural abnormalities.

This is a dose-dependent risk.1. Lower intelligence in valproate exposed children has been reported in doses > 800mg/day.
2. Autism spectrum disorder may be increased in children exposed to valproate in utero.
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| **Ongoing review whilst on valproate (non-pregnant)**  Discussed 1. Review with the treating neurologist is required at least once a year whilst on valproate
2. If pregnancy is planned, a timely appointment with the treating neurologist will ensure a discussion

(including switching to an alternative treatment before conception if possible) before stopping contraception. |
| **Unplanned pregnancy on valproate.**  Discussed 1. Urgent review with the treating neurologist and GP
2. Anti-epileptic drugs should not be abruptly stopped, as there is a risk of seizures
3. The risk period for structural abnormalities is in the first twelve weeks, but the risk of effects on intelligence is probably present through-out the pregnancy.
4. Discussion with the treating neurologist
	1. Is there an ongoing need for valproate?
	2. Can it be further reduced or substituted with another anti-epileptic drug?
	3. Have other possibly effective anti-epileptic drugs been properly trialled?
5. Individual instructions

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| Patient’s (or carer’s) name: …………………………………………………………………………………………………………………………………………………Signature: Date: / / Prescriber’s name: Signature: Date: / / *A copy of the completed and signed form shall be uploaded into patient notes.**Provide copy of this form to the GP* *Provide copy of this form to the patient, or to their parent/legal guardian or person capable of giving consent on behalf of patients who are minors or without the capacity to make an informed decision.**This form expires 12 months from this date. A new form should be completed at each annual review.* |

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