Medicines & Healthcare products Regulatory Agency

MHRA

Antiepileptic drugs: review of safety of use during pregnancy

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Contents

1 Plain Language Summary

Key message:

The Commission on Human Medicines has reviewed the available safety data for epilepsy medicines during pregnancy. This review was initiated in the context of the known harms of valproate in pregnancy.

The overarching findings of the review are that lamotrigine (brand name Lamictal) and levetiracetam (brand name Keppra) are the safer of the reviewed antiepileptic drugs during pregnancy because they are not linked with an increased risk of birth abnormalities compared with the general population. The available information also does not suggest an increased risk of the child having difficulties with learning or thinking ability but further data are needed to draw firm conclusions. Doctors or specialist epilepsy nurses should use this information when discussing treatment options with women and girls with epilepsy when starting treatment and at routine recommended annual review and with women who are planning a pregnancy.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK and ensuring their safety, quality and effectiveness. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. The Commission on Human Medicines advises government ministers and the MHRA on the safety, efficacy and quality of medicines.

In our public assessment reports, we discuss evidence-based reviews of safety issues linked with a particular medicine or group of medicines.

This report presents our review of studies in animals and in women who are pregnant to assess the safety of epilepsy medicines use during pregnancy.

About epilepsy

Epilepsy is a condition that affects the brain. When someone has epilepsy, it means that they have a tendency to have epileptic seizures.

There are many different types of epilepsy. These can have different causes, including a person's genetics, a structural change in the brain, or as a result of other health conditions.

It is difficult to know exactly how many people have epilepsy but it is estimated that it affects more than 600,000 people in the UK. That means around 1 in every 100 people in the UK has seizures or needs epilepsy medicines.

Epilepsy medicines (also known as antiepileptic drugs and antiseizure medicines) are medicines that treat epilepsy. More than 20 different epilepsy medicines are available. They aim to prevent or reduce the number of seizures someone has. For around 2 in 3 people with epilepsy, their seizures are controlled with one or more epilepsy medicines.

Epilepsy and pregnancy

Epilepsy is a long-term condition and so people can be on medicines for a long time. Every year in the UK around 2,500 women with epilepsy have a baby. Understandably there are many concerns that a woman will have when she begins to plan a pregnancy. These include how her epilepsy might affect her chance of becoming pregnant, how the pregnancy might affect her epilepsy, and also how her epilepsy medicine(s) may affect her unborn baby.

It is important that any woman with epilepsy who is planning a pregnancy or who becomes pregnant discusses their treatment options with their specialist, GP or specialist nurse. She should not stop taking her epilepsy medicines until she has their advice. This is because untreated epilepsy can cause harm to both the mother and her unborn baby.

Epilepsy medicines and the risks to the unborn baby

A birth abnormality, also known as a congenital disorder, is a condition a baby is born with. Congenital disorders can cause a range of different disorders, with some causing severe disability. Birth abnormalities can happen in any pregnancy, but certain things can increase the risk.

Compared with the general population, women with epilepsy who take antiepileptic drugs during pregnancy may have a higher risk of having a baby who is born with a birth defect or the antiepileptic drug may affect how the baby grows in the womb and the child's brain development (thinking, language, attention, social and behavioural skills). The risk to the unborn baby depends on many different things, including which epilepsy medicines are used during pregnancy. Some epilepsy medicines have a higher risk of harming a baby during pregnancy than others. The risk of harm to the baby may also be increased if a woman is taking a high dose of an epilepsy medicines or she is taking more than one epilepsy medicine, especially if this includes valproate or valproic acid.

Before planning a pregnancy, women are encouraged to have pre-conception counselling. Pre-conception counselling is an appointment, or series of appointments, with a doctor or nurse who knows about pregnancy and epilepsy. The aim is to review the person's epilepsy and epilepsy medicines. This discussion will take into account each woman's circumstances and help them decide which dose of which epilepsy medicine or combination of medicines is best for them and their baby during pregnancy.

Reason for the review

The epilepsy medicine, valproate or valproic acid (▼; brand names Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Syonell, Orlept, Valpal) can seriously harm an unborn baby if taken by the mother during pregnancy. It has been known for many years that valproate can cause physical birth abnormalities in the child. More recent studies have also shown that it can seriously affect the child's brain development which may become more apparent as they grow up, particularly in relation to learning and thinking abilities.

If 100 women take a valproate medicine during pregnancy about 10 of their babies will be born with physical birth abnormalities. This is compared with 2 to 3 out of 100 in the general population. And about 30 to 40 of the 100 children will go on to have disorders affecting their learning and thinking abilities, including autism. All doses of valproate carry a risk but the data support that the higher the dose of valproate, the higher the risks of birth abnormalities and effects on the child's brain development.

Due to the serious harms that can happen to the unborn baby, a number of restrictions have been made to prevent women with epilepsy from taking valproate during pregnancy. This is known as the valproate pregnancy prevention programme ('prevent').

The restrictions to the use of valproate in girls or women followed a review of the available safety data including studies in animals and women who are pregnant. At that time, similar reviews had not recently been done for the other epilepsy medicines. The Commission on Human Medicines recommended that the MHRA should review whether the available data raises any new safety concerns or changes current understanding about the safety of other epilepsy medicines during pregnancy.

Conclusions of the review

The available safety data supports the following conclusions:

<u>Physical birth abnormality</u>

- Lamotrigine and levetiracetam medicines are safer to use during pregnancy than other epilepsy medicines. Information supports that they do not increase the risk of physical birth abnormalities compared with the general population
- Carbamazepine (brand names Curatil, Tegretol), phenobarbital (brand names Phenobarbital Accord, Phenobarbital Elixir) or topiramate (brand name Topamax) use during pregnancy increases the risk of physical birth abnormalities compared with the general population

Epilepsy medicines where the data support an increased risk of having a baby born with a physical birth abnormality

General population	2 to 3 out of 100 babies
Carbamazepine	4 to 5 out of 100 babies
Phenobarbital	6 to 7 out of 100 babies
Phenytoin	about 6 out of 100 babies
Topiramate	4 to 5 out of 100 babies
Valproate	about 10 out of 100 babies

- Gabapentin (brand names Lecomig, Neurontin) and pregabalin (brand name Alzain, Axalid, Lecaent, Lyrica) - risks during pregnancy are not yet fully understood. Some data suggest that taking pregabalin during pregnancy may slightly increase the risk of a baby being born with physical birth abnormalities;
- Clobazam (brand names Frisium, Perizam, Tapcob, Zacco) and pregabalin - some research suggests that these medicines may slightly increase the risk of a baby being born with physical birth abnormalities. However, the research that is available does not allow firm conclusions to be reached and further data are needed; the risk of harming a baby cannot be confirmed or ruled out.
- Zonisamide (brand name Zonegran) – more data are needed to understand whether zonisamide use during pregnancy increases the chance of having a baby born with a birth abnormality.

Development of the brain

- Phenobarbital or phenytoin use during pregnancy increases the risk the child may have difficulties with learning and thinking ability. Although the exact risk is not known it is not as high as for valproate;
- For carbamazepine, lamotrigine and levetiracetam the available information does not suggest an increased risk of the child having difficulties with learning and thinking ability. However, the limited data for lamotrigine and levetiracetam mean an increased risk cannot be ruled out;
- For gabapentin, oxcarbazepine, pregabalin, topiramate and zonisamide more data are needed to understand whether use of these epilepsy medicines during pregnancy increases the chance of having a baby born with a learning or thinking disability.

Growth of the baby in the womb

- Phenobarbital, topiramate, or zonisamide use during pregnancy increases the risk of the baby being born smaller than expected compared with the general population.
- For lamotrigine and levetiracetam the information supports that use of these medicines during pregnancy does not increase the risk of the baby being born small for gestational age;
- For carbamazepine, gabapentin, oxcarbazepine, phenytoin and pregabalin the data are either limited or report inconsistent findings and therefore the possibility of an increased risk cannot be confirmed or ruled out.

For the medicines listed below there is not enough information on their use in pregnancy to make any conclusions about their safety when used during pregnancy. This means the risk of harming a baby cannot be confirmed or ruled out.

- Brivaracetam (brand name Briviact)
- Clonazepam (brand name Clonazepam Rosemont, Clonazepam Thame)
- Eslicarbazepine (brand name Zebinix)
- Ethosuximide (brand name Ethosuximide Aristo, Ethosuximide Essential Generics, Ethosuximide neuraxpharm)
- Lacosamide (brand name Vimpat)
- Rufinamide (brand name Inovelon)
- Perampanel (brand name Fycompa)
- Primidone (brand name Primidone SERB)
- Tiagabine (brand name Gabitril)
- Vigabatrin (brand name Kigabeq, Sabril)

2 Introduction

(See glossary for an explanation of the terms used in this report)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates. In our public assessment reports we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

The following report discusses our review of the non-clinical and clinical data relating to the safety of antiepileptic drugs during pregnancy.

Background

Epilepsy is one of the most common neurological conditions. Accurate estimates of incidence and prevalence of epilepsy are difficult to obtain as identifying everyone who may have epilepsy is challenging. It is estimated that more than 600,000 people in the UK have epilepsy and that every day 87 people in the UK are diagnosed with epilepsy. The estimated proportion of the UK population with active epilepsy (defined as having continuing seizures or a need for treatment) is around 1 in every 100 people in the UK. For around two-thirds of people with active epilepsy their epilepsy is adequately controlled by treatment with one or more antiepileptic drugs.

Epilepsy is also one of the most common neurological conditions in pregnancy and it is estimated that around 2500 infants are born to women with epilepsy every year in the UK (*ref UK Epilepsy and Pregnancy Register [http://www.epilepsyandpregnancy.co.uk/].* About one-third of women with epilepsy are in the reproductive age group (*Yerby 1994*).

The risks associated with the use of antiepileptic drugs during pregnancy are a significant concern for all women with epilepsy who are of childbearing potential. These risks need to be balanced against risks to the mother and the unborn baby of uncontrolled seizures. These discussions form an important part of the preconception counselling that should take place between a woman who is planning to start a family and her neurologist or general practitioner. It is also an important factor to be taken into consideration when initiating antiepileptic drug treatment in girls and women.

The available data support that there is an increased risk of major congenital malformations in children born to women with epilepsy treated with antiepileptic drugs during pregnancy and that the risk is greater at higher doses of antiepileptic drugs and with polytherapy compared with monotherapy. It is also recognised that some antiepileptic drugs taken by a mother during pregnancy can affect the physical and mental development of the unborn baby. However, the type and level of risk associated with use of antiepileptic drugs during pregnancy differs according to the specific antiepileptic drug(s) taken by the mother during the pregnancy. Where the available data are recognised to support an increased risk of either birth defects or effects on the unborn baby's growth and development, this is reflected in the product information that is provided with the medicine – the Summary of Product Characteristics (for use by healthcare professionals) and the Patient Information Leaflet, and may be accompanied by restrictions to its use.

Of the antiepileptic drugs that are authorised for use in the UK, valproate or valproic acid, which is indicated for use in epilepsy and bipolar disorders, is known to be associated with serious harm to the unborn baby if taken by the mother during pregnancy. The available data from epidemiological studies show that valproate is associated with a significant risk of birth defects (approximately 10 in 100 babies will have a birth defect compared with 2–3 in 100 babies in the general population) and developmental disorders (about 30–40 children in every 100 may have developmental problems including delays in early development such as talking and walking later, lower intellectual abilities, poor language skills and memory problems) in children born to women who take it during pregnancy.

The consistency and strength of the evidence for valproate supporting that its use during pregnancy is associated with serious harm to the unborn baby, has, in recent years, resulted in valproate being a major focus of European regulatory reviews of the safety of its use in women of childbearing potential and during pregnancy. The current requirement that girls and women of childbearing potential should only be treated with valproate if other antiepileptic drugs are ineffective or not tolerated and the need for women to be able to make informed choices about alternative antiepileptic drugs has increased the focus on the information available on the risks associated with use during pregnancy of other antiepileptic drugs.

Currently, valproate should not be used in girls (of any age) and women of childbearing potential unless there is no suitable alternative, as judged by a specialist experienced in the management of epilepsy or bipolar disorder. If valproate is the only effective or tolerated medicine, women and girls of childbearing potential should be enrolled in the Valproate Pregnancy Prevention Programme and a Risk Acknowledgement Form should be completed by the prescriber and patient every year at an annual specialist review.

The Epilepsies:diagnosis and management Clinical guideline [CG137] from the National Institute for Health and Care Excellence (NICE) recommends that in order to enable informed decisions and choice, women and girls with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children, breastfeeding, and menopause. In particular, it is recommended that there should be a discussion with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, concerning the risk of antiepileptic drugs causing malformations and possible neurodevelopmental impairments in an unborn baby.

To support informed decision-making, in July 2019 the Commission on Human Medicines (CHM) endorsed a proposal for a review of data from non-clinical and clinical studies relating to the safety of non-valproate antiepileptic drugs during pregnancy. The Commission on Human Medicines considered that certain antiepileptic drugs should be prioritised for review based on their place in national clinical guidelines, the extent to which they are used in the UK and the available safety data; these were carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide. Consequently, the available non-clinical and clinical data has been reviewed in order to determine whether the accumulating data raises any new safety concerns or changes the current understanding about the safety of use during pregnancy of these prioritised antiepileptic drugs.

Levetiracetam (brand name Keppra), which is another antiepileptic drug that is widely used in the UK, was not included amongst the antiepileptic drugs that were prioritised for review as the available data relating to safety of its use during pregnancy had been subject to a recent European review and updates to product information had already been made. However, the data considered during the European review and any more recent published epidemiological studies have been included in this public assessment report and formed the basis on which the advice of the Commission of Human Medicines was sought.

For completeness, clinical data in relation to a number of other antiepileptic drugs less commonly used in the UK has also been reviewed; these include brivaracetam, clobazam, clonazepam, eslicarbazepine, ethosuximide, lacosamide, perampanel, primidone, rufinamide, tiagabine and vigabatrin.

The table below provides information on number of prescription items dispensed in the UK in 2019 (Prescription Cost Analysis Data)

Table: Prescription Cost Analysis Data 2019 for antiepileptic drugs prioritised for review

Antiepileptic Drug	**Prescription items dispensed in the community in England in 2019***
Carbamazepine	2,274,769
Gabapentin	7,296,052
Lamotrigine	2,965,550
Levetiracetam	2,402,526
Oxcarbazepine	109,137
Phenobarbital	188,342
Phenytoin	675,597
Pregabalin	7,398,604
Topiramate	967,305
Zonisamide	164,243

* These figures include all prescription items dispensed in England for all indications so will include indications other than epilepsies

This public assessment report summarises the main evidence and key findings for the antiepileptic drugs considered in this review. It also presents the conclusions of the Commission on Human Medicines and its Neurology, Pain and Psychiatry Expert Advisory Group (NPPEAG).

The information and analyses contained in this report reflect evidence that was available at the time of the review in 2020. They are not intended to provide clinical advice. The MHRA will continue to monitor the safety of all medicines, however the information in this report will not be actively updated with new data or studies.

3 Summaries of main evidence and key findings

This section summarises the main evidence considered in this review along with the key findings. The information is presented for the following antiepileptic drugs in alphabetical order in sections 3.1 to 3.10 below – carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate and zonisamide. Section 3.11 summarises the data and findings on the antiepileptics less commonly used.

The available clinical data on the risk of major congenital malformations, neurodevelopmental disorders and delay, and also other reproductive toxic effects were taken from the published scientific literature and included meta-analyses and epidemiological studies in pregnancy registries, national birth registers, and population-based cohorts. The key findings from the main studies are presented in tabular form in Appendices 1 to 3.

For the other antiepileptic drugs that were less commonly used, the main findings are outlined in section 3.11. These medicines include brivaracetam, clobazam, clonazepam, eslicarbazepine, ethosuximide, lacosamide, perampanel, primidone, rufinamide, tiagabine and vigabatrin.

The data for diazepam, fosphenytoin, lorazepam, midazolam, thiopental sodium and stiripentol have not been reviewed given that the authorised indications for these antiepileptic drugs include status epilepticus, acute convulsions, refractory convulsive disorders or Dravet's syndrome.

The first step in developing and testing a new drug is non-clinical research and assessing the safety and efficacy in both *in vitro* models (such as cell cultures) and several animal species, including pregnant animals, prior to First in Humans. Once safety and efficacy profiles are established in these models the drug can then enter a clinical development programme. During its clinical development a drug is then tested on a range of people in clinical trials in order to generate information on safety and efficacy. Randomised controlled clinical trials are usually considered the best evidence to support a causal association. However pregnant women are generally excluded from participation in these trials for ethical reasons. This means that there is a lack of randomised clinical data on the effects of the drug in human pregnancy. Non-clinical studies conducted in pregnant animal models which are used as a surrogate, are therefore important to investigate the effects of a drug in pregnancy. This type of data provides insights on the drug's potential to interfere in human embryonic/fetal development because the mechanisms facilitating embryonic/fetal development are highly conserved through evolution and as a result there are many similarities between the response in the animal models and humans.

The review of non-clinical data in the published literature and company-sponsored studies, where available, considered teratogenicity, neurodevelopment and other reproductive toxic effects. The non-clinical neurodevelopmental studies were performed in pregnant animal models, neonatal animals, and neuronal cell cultures, and were designed to investigate the effects of the antiepileptic drugs on the offspring behaviour or tissues of the developing brain, focussing on the regions associated with the cognitive impairment reported in the children of women who used antiepileptic drugs during pregnancy (for example, general developmental delay, impaired language, and lowered IQ). A limited number of studies attempted to correlate the tissue changes in regions of the brain in animal models with changes in the behaviour of the offspring in the postnatal period.

Randomised controlled clinical trials are usually considered the best evidence to support a causal association. However, because pregnant women are rarely included in randomised controlled clinical trials, once a product is marketed the aim is to collect information on safety in pregnancy in order that better information can be provided to patients and healthcare professionals. This further information can be collected by a number of means including through spontaneous reporting schemes such as the Yellow Card Scheme in the UK, population-based birth registries of children born with congenital malformations, pregnancy registries and observational studies. Consistent findings from well conducted observational studies (or a meta-analysis thereof), where the design and methodology minimise the chance of bias and confounding, would be considered good evidence for a statistically significant increase in the risk of congenital malformations or the risk of adverse neurodevelopmental outcomes in the offspring of those who had taken antiepileptic drugs during pregnancy compared with those who had not. The data to support a causal association is considered limited where there mostly consistent but non-statistically significant findings from the available observational studies but these studies are either still at some risk of bias or they are too small to detect a statistically significant association should one exist, or there are consistent statistically significant findings from poor quality studies where the estimated magnitude of risk is such that it could not be explained by biases alone. Where there are either a limited number of studies, the available studies are too small or only poor quality studies are available then the data is considered insufficient to allow a conclusion to be reached on the likelihood of a causal association.

The conclusions of this assessment are based on an evaluation of the available non-clinical and clinical data. The assessment takes into account the methodology, including the quality of data, how it was collected, the existence of a non-exposed group or control group, the type of controls, and if possible, the inclusion of foetuses aborted due to malformation, etc. To allow a proper evaluation of the reliability of the data, the available studies must be of adequate scientific quality.

3.1 Carbamazepine

Carbamazepine (brand name Tegretol) is indicated for use in adults, adolescents, and children for the treatment of generalised tonic-clonic and partial seizures.

NICE guidance recommends that it can be used first line for the treatment of focal and generalised tonic–clonic seizures and also as adjunctive therapy in the treatment of focal seizures. Data from the Clinical Practice Research Datalink (CPRD) support that carbamazepine is among the most frequently prescribed antiepileptic drugs in women of childbearing age with epilepsy, but that its use in this group has been decreasingly steadily since 2010. These data also suggest it is among the more commonly prescribed antiepileptic drugs in pregnancy.

Congenital malformations

The available clinical data from meta-analyses (Meador et al, 2008, Weston et al, 2016, Veroniki et al, 2017a), pregnancy registries (Hernandez-Diaz et al, 2012, Campbell et al, 2014, Tomson et al, 2018, Vajda et al, 2019) and other large epidemiological studies (Petersen et al, 2017) involving around 9,000 pregnancies exposed to carbamazepine, of which around 6,000 pregnancies were exposed to carbamazepine in the first trimester, are generally supportive of an increased risk of major congenital malformations in association with carbamazepine exposure during pregnancy. The prevalence of major congenital malformations varies between 1.17% and 8% in the studies, likely reflecting the different study methodologies and populations studied. However, they generally appear to support a prevalence of around 4–5% and a risk of major congenital malformations following in-utero exposure to carbamazepine monotherapy that is higher than in the general population (2–3%) and higher than that seen in women with epilepsy who are untreated. Congenital malformations reported include cleft lip or palate, cardiac malformations, neural tube defects, hypospadias, genitourinary tract defects, skeletal malformations including club foot and polydactyly and respiratory and gastrointestinal malformations. These are broadly reflected in the current product information (the Summary of Product Characteristics for healthcare professionals and the Patient Information Leaflet).

The clinical data that is available to inform on the risk of polytherapy including carbamazepine (Meador et al, 2008, Veronika et al, 2017a) supports what is already known, which is that antiepileptic drug polytherapy is associated with a greater risk of major congenital malformations. However, it does not allow determination of the extent to which carbamazepine may contribute or even drive that risk. This is because the studies observing an increased risk associated with polytherapy involving carbamazepine also include other antiepileptic drugs that are considered to be associated with an increased risk of congenital malformations, such as valproate.

Where clinical studies have examined a dose-response, the findings are mixed; the larger studies are more supportive of an increased risk with increasing doses of carbamazepine (Tomson et al, 2018, UKEPR) but other smaller studies are not (Hernandez Diaz et al, 2012, Samren et al, 1997). The possibility of a dose-dependent risk is already reflected in the carbamazepine Summary of Product Characteristics.

Non-clinical studies in the published scientific literature in pregnant rats and mice report treatment-related congenital malformations in both rodent species (Sullivan and McElhatton,1977; Paulson et at., 1979; El-Sayed et at., 1983; Eluma et at., 1984; Vorhees et at.,1990; Finnell et al, 1995; Bennett GD, et al. 1996; El Shama, S., et al, 2015). The increased malformations observed in mice occurred at plasma concentrations relevant to the human therapeutic dose. Therefore, based on the currently available non-clinical data the risk of a teratogenic effect following therapeutic use in humans cannot be excluded.

Neurodevelopmental disorders and delay

Clinical data on the effects of prenatal exposure to carbamazepine and the risk of neurodevelopmental disorders is available from meta-analyses (Banach et al, 2010, Bromley et al, 2014 and Veroniki et al, 2017b) and a number of other epidemiological studies not included in these meta-analyses (Forsberg et al. 2011, Christensen et al, 2013, Deshmukh et al. 2016, Elkjær et al. 2018, Cohen et al, 2019, Christensen et al, 2019, Huber-Mollema et al, 2020).

Where studies have examined effects on intelligence quotient (IQ), there are conflicting results from some of the individual studies compared with the findings of the meta-analyses. Some recent prospective observational studies (Cohen et al, 2019 (61 children exposed to carbamazepine) and Huber-Mollema et al, 2020 (32 children exposed to carbamazepine)) have reported lower scores for IQ, specific components of the Children's Memory Scale (such as Learning Index), or specific components of neuropsychological development (visuomotor precision) in children whose mothers took carbamazepine during pregnancy compared with children whose mothers did not. Similar findings were not seen in the meta-analyses (Banach et al, 2010 (83 children in the carbamazepine group) and Bromley et al, 2014 (150 children in the carbamazepine group)) that included other prospective observational studies. These differences may reflect the different methodologies and designs in the individual studies and limitations such as the potential for residual confounding and lack of a comparison to women with epilepsy in some studies.

The meta-analyses by Bromley et al, 2014 and Veroniki et al, 2017b and the studies by Christensen et al, 2013 and 2019 have examined the effect of use of carbamazepine during pregnancy on outcomes including symptoms or diagnoses of autism spectrum disorders or attention deficit hyperactivity disorder (ADHD) in children whose mothers used carbamazepine during pregnancy. The largest studies are those by Christensen et al, 2013 (386 children exposed to carbamazepine) and 2019 (423 children exposed to carbamazepine), which examined the risk of autism spectrum disorders and ADHD, respectively. The studies by Christensen et al, and the meta-analyses do not suggest an increased risk of symptoms or diagnoses of autism spectrum disorders or ADHD following carbamazepine exposure during pregnancy.

Non-clinical studies in rodents from the published scientific literature have reported evidence of neurodegenerative changes that persist long into the postnatal period in regions of the developing brain associated with memory and learning (for example, hippocampus, cortex cerebri, and amygdala). These regions are implicated in the learning impairments observed in antiepileptic drug exposed children (Gonzalez-Maciel et al, 2020; Elshama S et al, 2015; Aberg E et al, 2013; Manent JB, et al, 2007; Araújo, I.M et al, 1988). There were limitations in the study designs employed and only a few investigated the effects of carbamazepine on the behaviour of the exposed offspring. These limited behavioural assessments reported no evidence of an effect on behaviour even when neurodegenerative changes were present (Aberg E et al, 2013). Overall uncertainty remains over the relevance of these non-clinical findings to the effects reported clinically.

Other reproductive toxic effects on the fetus or neonate

Clinical data on reproductive toxic effects are limited and the findings are mixed. Individual pregnancy registry and population-based cohort studies have reported increased risks of fetal loss with carbamazepine compared with unexposed women with epilepsy (Artama et al, 2013, Trivedi et al, 2018). However, the meta-analysis by Veroniki et al, (2017a) that included data on 3,911 carbamazepine monotherapy exposed pregnancies did not support an increased risk of fetal loss compared with unexposed women with epilepsy (OR 1.25, 95% credible intervals 0.73 to 2.36).

Two individual studies in national birth registers (Almgren et al, 2009, Margulis et al, 2019) were not included in the meta-analysis and have suggested reduced fetal head circumference following carbamazepine exposure. It is of note that the head circumferences observed in the studies by Almgren et al, and Margulis et al, likely remain within the normal range and therefore suggest only a very small effect of carbamazepine. These data do not suggest an increased risk of microcephaly. The meta-analysis by Veroniki et al, which did not include the studies by Almgren et al, and Margulis et al, did not support an increased risk of prenatal growth retardation (OR 1.15, 95% CrI 0.77 to 1.67) based on data from 2,897 carbamazepine monotherapy exposed pregnancies.

Non-clinical studies from the published scientific literature have shown reproducible evidence of intrauterine growth restrictions/delayed growth in rodents (e.g. reduced mean fetal body weights, reduced crown-rump length and delayed bone growth [length and size]) (Vorhees et al, 1990, El-Gaafarawi and Abouel-Magd, 2015, Elshama et al, 2015; Jose, M., et al, 2017). The lowest maternal plasma concentrations of carbamazepine associated with these findings was not reported therefore the relevance to the human therapeutic doses are unknown (El-Gaafarawi and Abouel-Magd, 2015).

Key findings for carbamazepine

Overall the available clinical and non-clinical data support the following key findings for carbamazepine:

- A large amount of post-marketing data exist on the risk of birth defects following the use of carbamazepine during pregnancy with the available studies involving around 9,000 pregnancies exposed to carbamazepine, of which around 6,000 were exposed in the first trimester. These data support that 4–5% of children exposed to carbamazepine monotherapy during pregnancy have congenital malformations. The risk is higher than that in babies born to mothers with epilepsy who were not exposed to antiepileptics during pregnancy, appears to be dose-dependent, and increases with antiepileptic drug polytherapy;
- The available clinical data on neurodevelopmental outcomes do not suggest an increased risk of neurodevelopmental disorders or delay. Limited non-clinical data reported evidence of an effect on the developing nervous system in rodents, however, the data are not sufficient to confirm a developmental neurotoxic potential.
- The findings from clinical studies examining fetal loss and fetal growth retardation are inconsistent and the non-clinical studies report that use of carbamazepine affects rodent fetal growth. Overall, the available evidence is inconclusive and the risks remain uncertain.

3.2 Gabapentin

Gabapentin (brand name Neurontin) is indicated for:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation in adults, adolescents aged 12 year and above;
- adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

It is also indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

NICE guidance recommends that it can be used as adjunctive treatment in focal seizures. Data from the CPRD suggests that among the prioritised antiepileptics drugs that gabapentin is one that is commonly initiated in women of childbearing age with epilepsy and also that it is among the most commonly prescribed antiepileptic drugs in pregnancy.

Congenital malformations

The available data from clinical studies remains relatively limited. The larger clinical studies are those from the North American Antiepileptic Drug pregnancy registry (Hernandez-Diaz 2012, NAAED, 2019), the Swedish National Birth Registry (Kallen et al, 2013) and a study using prospective data from teratology information services (Fujii et al, 2013). None of these studies are suggestive of an increased risk of congenital malformations in association with use of gabapentin during pregnancy. However, the numbers exposed in each of these studies and the total overall numbers of exposed pregnancies (around 600 first trimester exposed pregnancies) remains relatively low and do not allow robust conclusions to be drawn.

A meta-analysis by Veroniki et al, 2017a also did not suggest an increased risk of overall major congenital malformation with gabapentin use during pregnancy. However, gabapentin was found to be associated with statistically significantly more cases developing cardiac congenital malformations compared to the control group (odds ratio (OR) 5.98; 95% confidence interval (CI): 1.37-19.73) and hypospadias compared to the control group (OR, 16.54; 95% CI 2.50-121.70). These studies involved a very limited number of pregnancies (cardiac malformations: 2 studies involving a total of 45 exposed pregnancies, hypospadias: 1 study involving 39 exposed pregnancies) and further data are needed to determine whether this is a true effect.

The available non-clinical data from the published scientific literature, reports malformations in mice, however these findings are contradicted by the results of unpublished regulatory Good Laboratory Practice compliant studies in pregnant mice, rats and rabbits which did not detect evidence of teratogenicity in the exposed offspring at plasma concentrations equal to and above those used in the published studies. The Good Laboratory Practice studies are well designed for the purposes of detecting teratogenic effects of substances.

The risk of malformations with gabapentin therefore remains uncertain and further data are needed to inform our understanding.

Neurodevelopmental disorders and delay

The available clinical studies include a nationwide population-based cohort study using French national healthcare databases (Blotiere et al, 2020). This study provided data on 378 children exposed to gabapentin in utero and did not suggest that gabapentin was associated with an increased risk of neurodevelopmental disorders, pervasive developmental disorders, mental retardation or visits to a speech therapist.

Data are also available from a cross-sectional epidemiological study which retrospectively enrolled children from the UK Epilepsy and Pregnancy Registry (Bromley et al, 2016). However, the numbers for gabapentin were very low. Primary outcome data relating to 14 children exposed to gabapentin are reported but given the small size of the group they were not further investigated in the statistical analysis. Gabapentin was also included in the meta-analysis conducted by Veroniki et al, 2017b and this did not suggest a statistically significant increased risk of adverse neurodevelopmental outcomes in children associated with exposure to gabapentin in utero. However, the number of children exposed to gabapentin in utero was very limited and so overall no conclusions can be reached about the risk of adverse neurodevelopmental effects with gabapentin.

Non-clinical studies in the published scientific literature in rodents showed neurodegenerative changes in the cerebral cortex and hippocampus of fetuses exposed to gabapentin during early and mid-pregnancy (Prakash et al, 2008 and Badawy et al, 2019). However, limitations in the design of these studies make them insufficient to determine the effects of gabapentin on the developing nervous system. An unpublished Good Laboratory Practice compliant study in pregnant rats showed non-dose-related behavioural changes in the performance of the offspring during tests of activity and emotionality but the changes were not statistically significantly different from those of the control animals. Overall, the non-clinical data does not provide clear evidence that exposure to gabapentin during pregnancy adversely affects the development of the central nervous system.

Other reproductive toxic effects on the fetus or neonate

The available clinical studies (Fujii et al, 2013, Killic et al, 2014, Hernandez-Diaz et al, 2017) do not allow for firm conclusions to be reached. Some studies suggest that gabapentin use during pregnancy may result in an increased risk of preterm birth and prenatal growth retardation but these tend to include a small number of gabapentin exposed pregnancies. In the study with the largest number of pregnancies exposed to gabapentin monotherapy (Hernandez-Diaz et al, 2017; 153 gabapentin exposed pregnancies) the risk of the baby being born small for gestational age with gabapentin was not statistically significantly different from the risk with another antiepileptic drug (lamotrigine). Similarly, a recent meta-analysis (Veroniki et al, 2017a; 76 gabapentin exposed pregnancies) did not suggest an increased risk of on prenatal growth retardation and preterm birth following gabapentin use during pregnancy.

Non-clinical data from unpublished regulatory-compliant company-sponsored studies and from published studies have reported fetal growth retardation characterised as reduced fetal weights and crown-rump length in mice offspring (published studies [Prakash et al, 2008; Afshar M, Golalipour MJ 2008; Afshar M, et al, 2009]); delayed skeletal development in rat and mice offspring, and reduced birth weights in male rat offspring (unpublished regulatory-compliant studies) following exposure during pregnancy. The fetal growth retardation observed in the regulatory compliant studies occurred at doses approximately 1 to 5 times the human therapeutic dose.

Key findings for gabapentin

Overall the available clinical and non-clinical data support the following key findings for gabapentin:

- A moderate amount of clinical data exist on the risk of birth defects following the use of gabapentin during pregnancy with the available studies only involving around 600 pregnancies exposed to gabapentin in the first trimester. Overall, the limitations of the available clinical and non-clinical data do not allow any firm conclusions to be drawn. The risk remains uncertain and further data are required;
- Very limited clinical data exist on the risk of neurodevelopmental outcomes and this risk remains unknown. Limited non-clinical data report some evidence of an effect on the developing nervous system in rodents, however, the data are not sufficient to determine a developmental neurotoxic potential.
- A moderate amount of clinical data show conflicting findings with regards to effects on fetal growth. Non-clinical data report that the use of gabapentin during pregnancy is associated with adverse effects on fetal growth and development in rodents. Overall, the available data do not allow any firm conclusion to be drawn and the possibility of an effect on prenatal growth cannot be ruled out.

3.3 Lamotrigine

Lamotrigine (Lamictal) is indicated for use in adults and adolescents aged 13 years and above for:

- adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures;
- seizures associated with Lennox-Gastaut syndrome. Lamotrigine is given as adjunctive therapy but may be the initial antiepileptic drug to start with in Lennox-Gastaut syndrome.

It is also indicated for use in children and adolescents aged 2 to 12 years for:

- adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome;
- monotherapy of typical absence seizures.

NICE guidance recommends that it can be used as first line or adjunctive treatment for generalised tonic-clonic, absence or focal seizures and also as adjunctive treatment in tonic or atonic seizures.

CPRD data show that in women of childbearing age, lamotrigine is the antiepileptic drug that is most commonly prescribed and also most commonly started for the treatment of epilepsy. It is also among the most commonly prescribed antiepileptic drugs in pregnancy.

Congenital malformations

The review of clinical data on the risk of major congenital malformations with lamotrigine included data from meta-analyses (Meador et al, 2008, Weston et al, 2016, Veroniki et al, 2017a) and other large epidemiological studies which included pregnancies exposed to lamotrigine monotherapy (Cunnington et al, 2011, Petersen et al, 2017, Tomson et al, 2018, Vajda et al, 2019). Together these meta-analyses and studies included more than 12,000 pregnancies where lamotrigine monotherapy was used, including more than 9,000 in which lamotrigine was used in the first trimester These studies included comparisons with pregnancy outcomes in women without epilepsy, and in women with epilepsy who were not treated with antiepileptic drugs. The results from these meta-analyses and other studies consistently indicated that exposure to lamotrigine monotherapy during pregnancy is not associated with an increased risk of major congenital malformations at usual maintenance doses. The largest meta-analysis considered in this review included 6,290 pregnancies exposed to lamotrigine compared with pregnancies in women with epilepsy not exposed to antiepileptic drugs and there was no increased risk of major congenital malformations. The odds ratio for major congenital malformations was 0.96 (95% credible intervals 0.72 – 1.25). The risk ratio in this meta-analysis was 1.07 (95% CI 0.64 – 1.77) (Weston et al, 2016). The latest data on 2,514 exposed pregnancies from the International Registry of Antiepileptic Drugs and Pregnancy (EURAP) reported a major congenital malformation rate of 2.9% for lamotrigine (74/2,514) (Tomson et al, 2018).

The UK product information for lamotrigine recommends that the usual maintenance dose is 100 – 200 mg, although it notes that 500 mg per day has been required by some patients to achieve desired response. Studies investigating the effect of lamotrigine dose on the risk of major congenital malformations have shown conflicting results. A study in the International Lamotrigine Pregnancy Registry (Cunnington et al, 2011) reported no evidence of an increase in the rate of major congenital malformations after first trimester use of lamotrigine monotherapy (n=1,523) at doses increasing in 100 mg increments, although there was little use of daily doses above 600mg (n=44). A population-based cohort study using data from Danish health registers found no difference in major congenital malformation risk in a pre-planned analysis that evaluated the risks associated with first trimester mean daily doses of lamotrigine of 250 mg or lower (n=766) or higher than 250 mg (n=253) (Mølgaard-Nielsen and Hviid 2011). A study using data from the Australian Register of Antiepileptic Drugs in Pregnancy (APR), including pregnancies with use of lamotrigine monotherapy in the first trimester (n=406), did not find an association between lamotrigine dosage and risk of major congenital malformations (Vajda et al. 2019). However, a study using data from EURAP reported that the prevalence of major congenital malformations was 4.3% (28/644) for doses of lamotrigine higher than 325 mg per day compared with 2.5% (46/1,870) for doses of lamotrigine 325 mg per day or lower, odds ratio 1.68 (95% CI 1.01 – 2.80) (Tomson et al, 2018).

The assessment of the reproductive and developmental effects of lamotrigine in non-clinical studies is limited by the induction of maternal toxicity at human therapeutic doses and consequently its effects at higher exposures has not been performed. However, acknowledging such limitations, the non-clinical evidence reports that lamotrigine at doses relevant to human therapeutic doses is not teratogenic in rodents and rabbits. The absence of teratogenicity provides some reassurance over the use of lamotrigine in pregnancy but caution is required due to the limitations caused by the dosing restrictions.

Neurodevelopmental disorders and delay

Epidemiological studies and meta-analyses have investigated outcomes including measures of intelligence, developmental outcomes, and symptoms or diagnoses of autism spectrum disorders or ADHD (Veroniki et al, 2017b, Bromley et al, 2014, Deshmukh et al. 2016, Christensen et al, 2013, Elkjaer et al. 2018, Christensen et al, 2019, Cohen et al, 2019, Huber-Mollema et al, 2019 and 2020, Richards et al. 2019, Blotière et al. 2020, Husebye et al. 2020). Overall, the available clinical data do not indicate a negative impact of lamotrigine on these outcomes.

For the outcome of autism spectrum disorders, the data for lamotrigine were not completely consistent, with some studies reporting increases in the risk of autism spectrum disorders and similar outcomes, but with different estimates of the size of the increase. The largest single study that investigated autism spectrum disorder outcomes, by Christensen et al. 2013 (1383 children exposed to lamotrigine in utero), did not indicate an increase in risk in children whose mothers took lamotrigine during pregnancy, compared with children whose mothers did not take antiepileptic drugs during pregnancy, when adjusted for variables including maternal age, parental psychiatric history, gestational age, and sex. Some studies have reported potentially increased risks of autistic spectrum disorder outcome, or of poorer levels of early child development in terms of social and language skills, however some studies lacked precision or were potentially subject to residual confounding, or to bias where the outcomes were reported by those with knowledge of the child's antiepileptic drug exposure status, and these data are not sufficient to confirm a causal association with lamotrigine..

Non-clinical studies have reported that exposure to lamotrigine during pregnancy and also in juvenile rats can induce some neurobehavioural effects at doses relevant to human therapeutic doses.

Other reproductive toxic effects on the fetus or neonate

Overall, the available clinical data from epidemiological studies (Hernandez Diaz et al, 2014, Hernandez-Diaz et al, 2017, Killic et al, 2014, Trivedi et al, 2018, Bech et al, 2018, Vajda et al, 2018, Danielsson et al, 2019) and the meta-analysis by Veroniki et al. (2017a) do not suggest that lamotrigine monotherapy is associated with an increased risk of combined fetal loss, prenatal growth retardation, or preterm birth. The majority of the data come from studies including between 2,000 and 3,000 pregnancies where lamotrigine monotherapy was used and which were included in the meta-analysis by Veroniki et al. (2017a) for different reproductive outcomes. In this meta-analysis the odds ratio for combined fetal loss was 1.38 (95% CrI, 0.70 – 2.88), the odds ratio for prenatal growth retardation was 0.90 (95% CrI, 0.56 – 1.42)., and the odds ratio for preterm birth was 1.05 (95% CrI, 0.70 – 1.48). Whilst some individual studies, including some which contributed to the meta-analysis by Veroniki et al. (2017a), did report an increased risk of either spontaneous abortion (Trivedi et al, 2018) or preterm birth (Killic et al, 2014), these have some important limitations such as the possibility of residual confounding and/or low numbers of exposures.

Data from non-clinical studies report that increased incidences of reduced fetal body weights and skeletal variations in embryofetal development studies have been observed in rodents as well as increases in incidence of fetal and postnatal mortality, but these effects were observed in the presence of, and could be attributed to, maternal toxicity. Similar to the findings for teratogenic effects, the limited picture caused by the dosing restrictions mean that caution is required with regards to the interpretation of these data.

Key findings for lamotrigine

Overall the available clinical and non-clinical data support the following key findings for lamotrigine:

- Studies involving more than 12,000 pregnancies exposed to lamotrigine consistently show that lamotrigine at the usual maintenance doses recommended in the product information is not associated with an increased risk of major congenital malformations. Non-clinical data do not report a teratogenic effect at human therapeutic doses.
- The available clinical studies on neurodevelopmental outcomes do not suggest an increased risk of neurodevelopmental disorders or delay, however, the limitations of the data mean an increased risk cannot be definitively excluded. Non-clinical data report some neurobehavioural effects but the clinical relevance of these are unknown.
- A large amount of data from clinical studies examining the effects of lamotrigine on fetal growth and development do not support adverse effects following use of lamotrigine during pregnancy. Non-clinical data report that lamotrigine can produce effects on fetal growth at human therapeutic doses but this appears to be due to toxic effects in the mother and the clinical relevance is unclear.

3.4 Levetiracetam

Levetiracetam (brand name Keppra) is indicated for use as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults and adolescents aged 16 years and older. It is also indicated as adjunctive therapy in the treatment of:

- partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 4 years and older;
- myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy;
- primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy.

NICE guidance recommends that it can be used as first line or adjunctive treatment for myoclonic seizures and also as adjunctive treatment in generalised tonic-clonic or focal seizures.

Congenital malformations

The review considered clinical data from meta-analyses of published studies and epidemiological studies from pregnancy registries of antiepileptic drugs (Weston et al, 2016, Veroniki et al, 2017a, Tomson et al, 2018, Vajda et al, 2019), which included data on more than 1800 pregnancies exposed to levetiracetam monotherapy, of which more than 1500 exposures occurred during the first trimester. These studies consistently suggest that in-utero exposure to levetiracetam monotherapy is not associated with an increased risk of major congenital malformations.

The largest of these studies reported data on 599 levetiracetam exposed pregnancies from the International Registry of Antiepileptic Drugs and Pregnancy (Tomson et al, 2018) and 450 levetiracetam exposed pregnancies from the North American Antiepileptic Drugs Pregnancy Registry (Hernandez-Diaz et al, 2012); major congenital malformation rates of 2.8% and 2.0% respectively were reported and were not statistically significant increased compared with the control groups in these studies.

Neurodevelopmental disorders and delay

The available clinical data on the risk of neurodevelopmental disorders with levetiracetam is extremely limited and involves data on around 100 children (Shallcross et al, 2011, Bech et al, 2018, Huber-Mollema et al, 2019 and 2020). Levetiracetam was also included in the meta-analysis by Veroniki et al, (2017b). The available data do not suggest an increased risk of cognitive developmental delay, psychomotor developmental delay and autism/dyspraxia. However, as the numbers of exposures remains limited this cannot be concluded definitively and so it is important that any emerging data is kept under close review.

Other reproductive toxic effects on the fetus or neonate

The available clinical data from epidemiological studies (Killic et al, 2014, Trivedi et al, 2018, Bech et al, 2018, Vajda et al, 2018, Danielsson et al, 2019 and Margulis et al, 2019) and the meta-analysis by Veroniki et al. (2017a) including data on more than 1,800 pregnancies consistently suggest that levetiracetam monotherapy is not associated with an increased risk of fetal loss, prenatal growth retardation, or preterm birth.

Key findings for levetiracetam

Overall the available clinical data support the following key findings for levetiracetam:

- Clinical studies involving more than 1,800 pregnancies exposed to levetiracetam monotherapy (including more than 1,500 pregnancies exposed to levetiracetam in the first trimester) do not suggest an increase in the risk for major congenital malformations;
- Available clinical studies do not suggest an increased risk of neurodevelopmental disorders or delay associated with in-utero exposure to levetiracetam but the data are very limited meaning the risks remain uncertain and the possibility of an increased risk cannot be excluded;
- Clinical studies examining the effects of levetiracetam on fetal growth and development do not suggest that levetiracetam is associated with adverse effects.

3.5 Oxcarbazepine

Oxcarbazepine (brand name Trileptal) is indicated as monotherapy or adjunctive therapy in adults and children aged over 6 years of age with partial seizures with or without secondary generalised seizures.

NICE guidance recommends that oxcarbazepine can be used first line for generalised tonic-clonic seizures and also as first line and adjunctive treatment for focal seizures.

Congenital malformations

Overall, the available clinical data does not suggest an increased risk of major congenital malformations associated with oxcarbazepine during pregnancy. However, the number of exposures is more limited than that for some of the other antiepileptic drugs with around 800 total exposed pregnancies including around 600 first-trimester-exposed pregnancies.

The clinical data from meta-analyses, pregnancy registry studies and the larger epidemiological studies (Weston et al, 2016, Veroniki et al, 2017a, Tomson et al, 2018, data published on North American Antiepileptic Drug Pregnancy Registry website in 2019, Vajda 2019) which included data on around 800 pregnancies suggest that the prevalence of major congenital malformations associated with in-utero exposure to oxcarbazepine is 2–3% and is similar to that seen in the general population. These studies also suggest that the risk of malformations is not greater than that seen in women with epilepsy that are not exposed to antiepileptic drugs. The study by Tomson et al, 2018, which is the largest of the individual studies, compared the risk seen with oxcarbazepine to that seen with other individual antiepileptic drugs and these data do not suggest that the risk differs significantly from that seen with lamotrigine, levetiracetam or carbamazepine. For these other antiepileptic drugs that were used as comparators, the available clinical data for both lamotrigine and levetiracetam do not support an increased risk of major congenital malformations with either of these antiepileptic drugs when used at usual maintenance doses, however, the data for carbamazepine does support an increased risk of major congenital malformations.

There are some studies that report a higher prevalence of major congenital malformations (Kallen et al, 2013, Vajda et al, 2019) with oxcarbazepine. These studies include low numbers of oxcarbazepine exposed pregnancies – less than 50 pregnancies exposed to monotherapy in the first trimester.

It is also of note that oxcarbazepine is structurally similar to carbamazepine (it is structural analog of carbamazepine) but is metabolised differently in the body and therefore its side effect profile may differ to that of carbamazepine, which has been shown to be associated with an increased risk of major congenital malformations. Further data are needed to more fully inform the understanding of the risk of congenital malformations with oxcarbazepine and no definitive conclusions can be reached.

A regulatory-compliant company-sponsored study in pregnant rats reported an increased incidence of fetal malformations at human therapeutic doses (approximately 1.2 to 4 times the maximum human recommended dose)

Neurodevelopmental disorders and delay

Clinical data on the risk of neurodevelopmental disorders with oxcarbazepine is primarily driven by data from retrospective studies using Danish national registries (Bech et al, 2018, Christensen et al, 2013 and 2019) and the meta-analysis by Veroniki et al, 2017b.

Overall, these data are not supportive of a detrimental impact, as all three studies do not support any impact on school performance, nor do they suggest an increased risk of attention deficit hyperactivity disorder or autism spectrum disorder in children in association with oxcarbazepine use during pregnancy. Although the data from the Veroniki et al,

meta-analysis suggested a significantly increased risk of autism/dyspraxia (OR 13.51 [95% CrI 1.28–221.40]), this was based on limited data as is reflected in the very wide confidence interval. Furthermore, the increased risk of autism/dyspraxia was no longer statistically significant when a sensitivity analysis was conducted that only included studies considered to be at low risk of bias (OR 10.23 [95% CI 0.36–6.8x10^3]), suggesting that this is not a robust basis on which to reach a conclusion about an increased risk of autism.

Non-clinical data are limited in terms of the number and design of the studies that have investigated the effect of oxcarbazepine on the developing central nervous system (Araújo, IM et al, 2004 and Pavone A, Cardile V, 2003), however evidence of a neurodegenerative effect in the hippocampus of rat offspring, which persists long into the postnatal period has been reported. These offspring also had substantial changes in brain and body weights prenatally and postnatally (Gonzalez-Maciel et al, 2020). The clinical relevance of these recent findings are unclear due to limitations in the study design; however, they may be related to the results of a regulatory compliant company sponsored study in which behavioural changes (slightly reduced activity index) had been concluded to be associated with diminished body weight gain of the offspring as opposed to an effect on the central nervous system.

Other reproductive toxic effects on the fetus or neonate

The findings from clinical studies with regards to the risk of fetal death in association with in-utero exposure to oxcarbazepine are inconsistent. The meta-analysis by Veroniki et al, (2017a) does not support an increased risk of fetal loss, however, data from some studies in pregnancy registries (Artama et al, 2013, Trivedi et al, 2018) are suggestive of a trend towards an increased risk of fetal loss in association with oxcarbazepine exposure during pregnancy. However, these studies suffer from some limitations that preclude firm conclusions being reached. Equally there are other prospective studies in pregnancy registries that do not support an increased risk of fetal loss (Bech et al, 2014, Vajda et al, 2018).

Similarly, the data from clinical studies on the risk of intrauterine growth retardation show inconsistent results. The meta-analysis by Veroniki et al, (2017a) does not suggest an increased risk with oxcarbazepine (OR 0.99, 95% CI 0.56–1.76), while some individual studies (Artama et al, 2013, Killic et al, 2014) report findings that are suggestive of an adverse effect on prenatal growth and development. Artama et al, was associated with a statistically significant increased risk of babies being born small for gestational age but with no detrimental effects on birth weight. In contrast, the study by Killic et al, 2014 suggested an effect of oxcarbazepine on birth weight but no increased risk of babies being born small for gestational age. These conflicting findings along with the limitations of these studies mean that the available data do not provide a robust basis from which to draw conclusions.

Non-clinical data from studies in rats have reported developmental toxicity (embryolethality, growth retardation) in the offspring exposed to either oxcarbazepine or its active 10-hydroxy metabolite during pregnancy at doses relevant to human therapeutic doses.

Given the non-clinical data showing effects on fetal growth and conflicting clinical data it is important that any emerging data are carefully evaluated in order to better inform our understanding in this respect.

Key findings for oxcarbazepine

Overall the available clinical and non-clinical data support the following key findings for oxcarbazepine:

- A moderate amount of clinical data exist on the risk of birth defects following the use of oxcarbazepine during pregnancy, with the available studies only involving around 800 total exposed pregnancies including around 600 first-trimester-exposed pregnancies. Whilst these data do not suggest an increased risk of congenital malformations. the limited data coupled with the findings from non-clinical studies of teratogenic potential at human therapeutic doses do not allow the possibility of an increased risk of malformation to be definitively excluded;

- The limited available clinical data on the risk of neurodevelopmental outcomes following oxcarbazepine exposure during pregnancy do not suggest an increased risk, however, further data are required before an increased risk can be definitively ruled out. Non-clinical data are very limited but neurodegenerative effects have been reported.

- The findings from clinical studies are inconsistent and the risk remains uncertain. Non-clinical studies in rodents report that use of oxcarbazepine during pregnancy affects fetal growth.

3.6 Phenobarbital

Phenobarbital is indicated for the treatment and control of all forms of epilepsy, except absence seizures. However, it should only be used in the treatment of febrile convulsions in exceptional circumstances.

NICE guidance recommends that it can be used as adjunctive treatment in convulsive status epilepticus and may be considered for use by a tertiary epilepsy specialist in focal seizures when adjunctive treatment is not effective or not tolerated.

Congenital malformations

The clinical studies, which comprise data from three meta-analyses (Meador et al, 2008, Weston et al, 2016, Veroniki et al, 2017a) and other epidemiological studies (Veiby et al, 2014, Tomson et al, 2011 and 2018, Hernandez-Diaz et al, 2012), also support a teratogenic effect.

These clinical studies, involving around 1800 pregnancies exposed to phenobarbital (including 600 pregnancies exposed in the first trimester), show an increased risk of major congenital malformations following phenobarbital exposure compared with either unexposed women without epilepsy or unexposed women with epilepsy. While there is some variation in incidence rates with the largest meta-analysis by Weston et al, 2016 showing a prevalence of 7.1%, other studies broadly support incidence rates of malformations in offspring of phenobarbital exposed women of around 5–6%).

Across these studies not all the reported increased risks reached statistical significance, however, the data appear to broadly support an approximately 2–3-fold increase in risk (Weston et al, 2016, Relative Risk 2.84 (95% CI 1.57-5.13); Hernandez- Diaz et al, 2012, Relative Risk 2.9 (95% CI 1.4-5.8); Tomson et al, 2018 Odds Ratio 2.46 (95% CI 1.16-5.23); and Veroniki et al, 2017a Odds Ratio 1.83 (95% CI 1.35 -2.47)) compared to unexposed pregnancies. The study by Veiby et al, 2014 in the Norwegian Birth register did not show a statistically significantly increased risk of malformations with phenobarbital but this was a relatively small study (27 pregnancies exposed to phenobarbital monotherapy) and a higher risk cannot be excluded.

Data from Tomson et al, 2011 suggest a dose-dependent increase in the risk of major congenital malformations with a rate of 5.4% for doses lower than 150mg per day up to 13.7% for doses higher than 150 mg per day (OR 3.2; 95% CI 1.11 to 9.45, p=0.0316). Veiby et al, only reported on average phenobarbital dose (120mg per day) but the prevalence they observed (5.5%) appears in line with data from Tomson et al, 2018 (6.5%).

Studies consistently reported a higher rate of major congenital malformations in polytherapy compared to monotherapy (Meador 2008, Veroniki 2017a, Veiby 2014, Vajda 2014, Tomson 2018, Dean 2002), however, the details of the individual antiepileptic treatment that contributed to polytherapy were often not provided so it is not possible to determine to what extent phenobarbital contributes to the greater risk seen with polytherapy.

Non-clinical evidence regarding phenobarbital-induced malformations is limited to studies in mice from the published scientific literature. These studies have reported that phenobarbital exposure during pregnancy is associated with an increased risk of malformations in the offspring.

Neurodevelopmental disorders and delay

Overall, the data from clinical studies are suggestive of a possible adverse effect of pre-and postnatal phenobarbital exposure on neurodevelopment and IQ. Whilst some studies suggest the detrimental effects may weaken over time (Farwell 1990, Sulzbacher 1999, Thorp 1999 and 2003), in other instances they seemed to last into adulthood (Reinisch et al, 1995).

The meta-analyses of epidemiological studies (Bromley et al, 2014, Veroniki et al, 2017b) do not support an increased risk of adverse effects on neurodevelopment and delay, however, these meta-analyses include few studies that include relatively small numbers of exposed children and it was recognised by the authors that the absence of evidence should not regarded as evidence of safety.. There are well conducted prospective cohort studies including small numbers of subjects (<30 monotherapy exposures), that observed significant neurodevelopmental delay and detrimental effects on IQ in children whose mothers took phenobarbital monotherapy during pregnancy (Titze et al, 2008, Gopinath et al, 2015, van der Pol et al, 1991). Furthermore, longer-term postnatal treatment of a larger group of infants of >200 subjects (Farwell et al, 1990) was found to be associated with

statistically significant neurodevelopmental delay that appeared to weaken with time but a lower achievement score (WRAT-R) was still measurable a number of years later (Sulzbacher et al, 1999). A double-blind, randomised, placebo-controlled study by Thorp et al, 1999 including perinatal phenobarbital treatment (antenatal and neonatal) was associated with a significant reduction in both mental development index and psychomotor development index in the exposed children after a two year follow up when compared to offspring exposed to placebo. A publication describing results of two retrospective cohort studies using independent samples and matched controls of 33 and 81 adult men also found significant associations of prenatal phenobarbital exposure and lower IQ in both studies following use of different outcome measures (study 1: Wechsler Adult Intelligence Scale; study 2: Danish Military Draft Board Intelligence Test) (Reinisch et al, 1995). Other studies assessing outcomes following prenatal exposure at ages between 18 months and 7 years (Shankaran 1996, Shankaran 2002; Thorp 2003) based on primary randomised controlled trials, did not find a significant effect on neurodevelopment. However, a dose-dependent effect based on cumulative dosage was described in some studies (Reinisch et al, 1995, Gopinath et al, 2015) and it is possible that the total dosages used by Shankaran and Thorp are on the low side. It is of note that the studies examined the risk across a variety of indications and this may give further support to the likelihood of a true association.

Non-clinical studies in the published scientific literature have reported that exposure to phenobarbital during and soon after pregnancy can induce neurobehavioural effects in offspring and induce widespread apoptotic neurodegeneration in the brains of rodents. However, there are limitations to the data.

Other reproductive toxic effects on the fetus or neonate

Data from the meta-analysis by Veroniki et al, 2017a, showed that exposure to phenobarbital monotherapy or polytherapy during pregnancy was not associated with an increased risk of combined fetal loss or preterm birth when compared to the control groups, which is supported by a study by Tomson et al, 2015 examining data from the International Antiepileptic Drug and Pregnancy Registry. However, the meta-analysis did suggest that exposure to phenobarbital monotherapy during pregnancy was associated with a statistically significant increased risk of prenatal growth retardation (OR, 1.88; 95% CI, 1.07–3.32) and this is supported by data from the North American Antiepileptic Drug Pregnancy Registry (Hernandez-Diaz et al, 2017). Overall, the data are indicative of adverse effects on prenatal growth following in-utero exposure to phenobarbital.

Key findings for phenobarbital

Overall the available clinical and non-clinical data support the following key findings for phenobarbital:

- A large amount of data exist on the risk of birth defects following the use of phenobarbital during pregnancy with the available studies only involving around 1,800 pregnancies exposed to phenobarbital including around 600 exposed in the first trimester. The largest meta-analysis showed a prevalence of 7.1% for major congenital malformations and most individual studies support that 5-6% of children exposed to phenobarbital monotherapy during pregnancy suffer from congenital malformations. This risk is increased compared with children of mothers who were not exposed to antiepileptics during pregnancy (2-3% in general population) and appears be higher with increasing doses of phenobarbital. Non-clinical data are limited but also suggest phenobarbital may be teratogenic.
- Clinical data on neurodevelopmental outcomes following pre and postnatal exposures to phenobarbital is suggestive of possible adverse effects on neurodevelopment. Non-clinical data report possible neurobehavioural effects but limitations in the data exist.
- Clinical studies examining the effects of phenobarbital on fetal growth and development suggest that exposure to phenobarbital during pregnancy is associated with a higher risk of babies being born small for gestational age.

3.7 Phenytoin

Phenytoin (brand name Epanutin) is indicated for the control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

NICE guidance recommends that phenytoin can be used as adjunctive treatment for convulsive status epilepticus in hospital and may be considered on referral to tertiary care for the treatment of focal seizures.

Congenital malformations

Clinical studies involving more than 2,000 pregnancies exposed to phenytoin, including around 1,000 pregnancies exposed in the first trimester, show an increased risk of major congenital malformations following prenatal phenytoin exposure compared with either unexposed women without epilepsy or unexposed women with epilepsy (Meador et al, 2008, Hernandez-Diaz 2012 and 2019, Weston et al, 2016, Veroniki et al, 2017a, Tomson et al, 2018). While there is some variation in prevalence rates, authors of the more robust studies including the Cochrane analysis by Weston et al, and the meta-analysis by Meador et al, reported prevalence rates of major congenital malformations in the offspring of women exposed to phenytoin during pregnancy of around 6–7%, which is consistent with that seen in the study exploring data in the International Antiepileptic Drug and Pregnancy Registry (Tomson et al, 2018). While the prevalence observed in the North American Antiepileptic Drug Registry is much lower (2.6%; 95% CI 1.4 to 4.4), the prevalence of major congenital malformations in the internal control group of 1.1% (95% CI 0.5 to 2.0) is also lower than would be expected in the general population (2–3%) and therefore this may reflect a different approach to the identification of major congenital malformations within this registry.

Across these studies not all reported increased risks reached statistical significance, however, the data appear to broadly support an approximately 2-2.5 fold increased risk of major congenital malformations compared to pregnancies not exposed to antiepileptic drugs (Weston et al, Risk Ratio 2.4 (95% CI 1.42 – 4.08); Hernandez- Diaz et al, Relative Risk 2.6 (95% CI 0.9 -7.4); Tomson et al, Odds Ratio 1.93 (95% CI 0.78 – 4.75); Veroniki et al, Odds Ratio 1.67 (95% CrI 1.3 -2.17)) as well as an approximately 1.5-fold increased risk compared with pregnancies exposed to lamotrigine. A recent study in the Australian Pregnancy Registry (Vajda et al, 2019) did not show an increased risk of malformations with phenytoin but this was a small study only involving 88 phenytoin-exposed pregnancies with wide confidence intervals that did not exclude the possibility of an increased risk.

Studies that explore a dose-dependent risk are very limited but where this was studied (Nulman et al, 1997, Samren et al, 1997, Kaneko et al, 1999, Kaaja 2003, Hernandez-Diaz et al, 2012) the data do not consistently show an association between dose and risk of major congenital malformations. Of these studies, only Samren 1997 and Kaneko et al, 1999 reported a dose-effect. Samren conducted a very small study involving 33 phenytoin exposed pregnancies. Kaneko (132 exposed pregnancies), found a clear but not statistically significant positive trend between dose and incidence of malformation based on 132 phenytoin-exposed pregnancies. Overall, these data are inconsistent and too limited to draw conclusions on a dose-dependent risk of congenital malformations following phenytoin exposure in utero.

The data available to inform on the risk of polytherapy including phenytoin (Meador et al, 2008, Veronika et al, 2017a, Keni et al, 2008) does not allow determination of the extent to which phenytoin may contribute or even drive the increased risk seen with polytherapy because polytherapy included antiepileptic drugs known to cause malformations (such as valproate).

Non-clinical studies in pregnant rats, rabbits, and mice report that exposure during pregnancy resulted in fetal malformations and these occur at plasma concentrations relevant to human therapeutic doses. The defects observed in animals are similar to those seen with fetal hydantoin syndrome.

Neurodevelopmental disorders and delay

Although the available clinical data concerning neurodevelopmental disorders and delay are inconsistent there are some small, reasonably well-conducted studies that do support an adverse effect on neurodevelopment. Both meta-analyses (Bromley et al, 2014, Veroniki et al, 2017b) along with most of the individual epidemiological studies did not support an increased risk of adverse effects on neurodevelopment, cognitive outcomes or IQ in children whose mothers took phenytoin during pregnancy when compared to non-exposed control groups or those exposed to other antiepileptic drugs (Leavitt 1992, Wide 2002 Thomas et al, 2007, Thomas et al, 2008, Thomas et al, 2009, Forsberg et 2011, Gopinath et al, 2015, Cohen et al, 2019). However, some small, well-conducted clinical studies (less than 30 phenytoin exposures) showed a significant increased risk of serious adverse outcomes compared to control subjects including fetal hydantoin syndrome, effects on development (Rovet 1995, Arulmozhi 2006) and below average IQ (Hanson 1976, Scolnik et al, 1994).

Published scientific literature has reported that phenytoin exposure during pregnancy can induce behavioural abnormalities in animal offspring at plasma concentrations relevant to human therapeutic doses. It has also been reported in the published scientific literature that phenytoin can induce neurodegeneration in neonatal rodent brains following early postnatal exposure at plasma concentrations of phenytoin relevant to human therapeutic concentrations.

Other reproductive toxic effects on the fetus or neonate

The available clinical do not support a detrimental effect on fetal growth and development. The meta-analysis by Veroniki et al, 2017a found that phenytoin monotherapy was not associated with increased combined fetal loss or preterm birth when compared to controls; and it was associated with the lowest risk of impaired prenatal growth retardation among the investigated antiepileptic drugs. Hernandez-Diaz et al, 2017 also did not observe an increased risk of being small for gestational age (adjusted RR 0.8, 95% CI 0.5-1.25) for phenytoin compared with lamotrigine.

A further study by Trivedi et al, 2018 in the Kerala Pregnancy Registry investigated spontaneous fetal loss in pregnancies exposed to phenytoin compared with pregnancies in non-exposed women with epilepsy. Although the risk was statistically significantly increased compared to the untreated control group, there was no difference compared with a levetiracetam exposed group and the available data for the latter does not appear to support an increased risk of fetal loss.

One study (Dean et al, 2002) suggested that phenytoin use during pregnancy may be associated with an increased risk of neonatal withdrawal effects but this study included a small number of children.

Non-clinical studies in pregnant rats, rabbits, and mice report that phenytoin exposure during pregnancy can cause embryofetal death and decreased fetal growth.

Key findings for phenytoin

Overall the available clinical and non-clinical data support the following key findings for phenytoin:

- A large amount of post-marketing data exist on the risk of birth defects following the use of phenytoin during pregnancy with the available studies involving more than 2,000 pregnancies exposed to phenytoin (including around 1,000 pregnancies exposed in the first trimester). These data support that around 6% of children exposed to phenytoin monotherapy during pregnancy suffer from congenital malformations. This risk is increased compared with that in children of mothers who were not exposed to antiepileptics during pregnancy (2-3% in the general population). Non-clinical data report that phenytoin is teratogenic.

- The clinical studies report inconsistent findings with regards to the effect of phenytoin on the risk of neurodevelopmental disorders or delay. Non-clinical studies report that exposure during pregnancy at human therapeutic doses can cause neurobehavioural abnormalities. Overall, taken together the available non-clinical and clinical data are suggestive of possible adverse effects on neurodevelopment;

- A moderate amount of data from the available clinical studies examining the effects of phenytoin on fetal loss and fetal growth and development do not suggest that it is associated with adverse effects. However, the non-clinical studies report that use of phenytoin can affect fetal growth.

3.8 Pregabalin

Pregabalin (brand name Lyrica) is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation. It is also indicated in adults for the treatment of peripheral and central neuropathic pain and the treatment of generalised anxiety disorder (GAD).

NICE guidance recommends that pregabalin may be considered by the tertiary epilepsy specialist in the treatment of focal seizures if adjunctive treatment is not effective or not tolerated. Therefore, its use in epilepsy is likely limited and the product information reflects that the available data on pregnancy outcomes is also limited.

Prescribing trend data show that prescribing prevalence rates for pregabalin are high and have been increasing over time but this is reflective of the increasing use in the pain and anxiety indications. In June 2019, the rate was 75.94 prescriptions per 10,000 eligible women of childbearing age women (CPRD GOLD), making pregabalin the second most frequently prescribed antiepileptic drug in women of childbearing age among the drugs which have been prioritised for review. CPRD data also show that among the prioritised antiepileptic drugs it is the one that is most commonly prescribed in pregnancy. These data suggest that there is substantial use in women of childbearing potential and also during pregnancy.

Congenital malformations

Emerging unpublished data from a clinical study provide some suggestion of a slight increased overall risk of congenital malformations. However, at the time of publication of this report the study data are currently undergoing further evaluation at a European level.

In a retrospective cohort study, Blotière et al, 2019 used data from the French healthcare databases. This included data from 1,671 pregnancies exposed to pregabalin monotherapy of which 918 were considered exposed during first trimester, with the others discontinuing treatment prior to conception. This study examined rates of 23 specific malformations, so no overall rate of major congenital malformations was available. It identified potential signals of increased risk of coarctation of aorta (Odds Ratio 5.8 [95% CI 1.6 -14.9]) and craniosynostosis (Odds Ratio 8.1 [95% CI 1.7-23.7]), but no other increased risk was seen for any of the other 21 malformations studied. Given the lack of an overall malformation rate and the further limitations of this study (retrospective nature, potential for exposure misclassification, and small numbers of malformations) it does not allow any firm conclusions to be drawn about the risk of major congenital malformations associated with pregabalin.

Other smaller clinical studies show conflicting results. A multi-centre, prospective observational study by Winterfeld et al, provided data on 164 pregabalin exposed pregnancies (116 first trimester exposed pregnancies) and observed a higher rate of major birth defects in the pregabalin group (7/116 [6.0%]) compared to pregnancies in women not exposed to any medications known to be teratogenic or to any antiepileptic drugs (12/580 [2.1%]) to give an OR of 3.0 [95% CI 1.2–7.9], p=0.03). However, as the authors themselves acknowledged, this study includes a relatively small number of exposed pregnancies and suffers from a number of limitations and no robust conclusions can be drawn.

Patorno et al, 2017 conducted a cohort study nested in the US Medicaid Analytic eXtract (MAX) providing data on 477 pregnancies exposed to pregabalin in the first trimester and compared these to pregnancies of women not exposed to antiepileptics. The crude data suggested an increased risk of major congenital malformations (RR 1.80, 95% CI 1.26–2.58), which this was no longer statistically significant after the analyses were adjusted to take into account factors including age, race, comorbidities, and other medication.

Other clinical studies by Veiby et al, 2014 and Mostacci et al, 2017 contain less than 30 pregnancies exposed to pregabalin in the first trimester and provide very little data to inform our understanding.

Limited published non-clinical studies report of teratogenicity in rodents however, in company sponsored studies no teratogenicity was reported in rodents and rabbits at plasma concentrations far exceeding human therapeutic doses. In considering the conflicting data regarding the teratogenic potential of pregabalin, no firm conclusions can be drawn of its potential teratogenic effect..

Neurodevelopmental disorders and delay

The preliminary conclusion from review of emerging unpublished clinical data is that there was no evidence of an increased risk for attention deficit hyperactivity disorder, autism spectrum disorders and learning disabilities in pregabalin-exposed children. However, the study data are being further reviewed.

A nationwide population-based cohort study in French national healthcare databases by Blotiere et al, 2020 provided data on 1,627 children exposed to pregabalin. In this study pregabalin was not associated with an increased risk of neurodevelopmental disorders, pervasive developmental disorders, mental retardation, or visits to a speech therapist.

Non-clinical studies report on neurobehavioral effects in the offspring of rats given pregabalin during gestation and lactation but at doses which generated plasma concentrations higher than human therapeutic doses. Non-clinical studies also suggest that neurobehavioural effects can occur following dosing of juvenile rats at doses relevant to human therapeutic doses, however, reversibility has been observed upon discontinuation of dosing.

Other reproductive toxic effects on the fetus or neonate

Emerging unpublished clinical data found no statistically significant findings for small for gestational age, low birth weight and preterm birth outcomes, but these data are currently under review.

A study in the nationwide Swedish Medical birth register (Margulis et al, 2019) reported on the outcomes for 562 pregabalin exposed infants compared to those exposed to lamotrigine. Compared with infants exposed to lamotrigine, those exposed to pregabalin were reported to be born, on average, 1.1 days earlier (95% CI –3.0 to 0.8), an effect that was more notable in women with a diagnosis of epilepsy (–5.6 days, 95% CI –10.7 to –0.4); were 0.1 standard deviations lighter (95% CI –0.3 to 0.0); and had the same head

circumference. However, it is considered there is a strong possibility that residual confounding may have had an effect on the pregabalin analyses given the distinct profile of pregabalin users (younger, less well-educated and more likely to be obese or smokers).

Other smaller studies (Mostacci et al, 2018, Killic et al, 2014) reported on the outcomes of 14 and 18 pregnancies exposed to pregabalin, respectively. However, the very low numbers for pregabalin mean that no statistical analyses were conducted, and no conclusions can be reached with respect to the risk associated with pregabalin from either of these studies

Non-clinical studies report reduced fetal body weights in rats and rabbits following exposure to pregabalin during pregnancy but this occurred at plasma concentrations sufficiently higher than human therapeutic concentrations. Dosing of pregabalin during gestation and lactation induced offspring developmental toxicity in rats at exposures 5 times or greater than the maximum recommended human exposure.

Key findings for pregabalin

Overall the available non-clinical and clinical data support the following key findings for pregabalin:

- Data from the available clinical studies, including preliminary unpublished study data is suggestive of a slightly increased overall risk of congenital malformations but there is uncertainty in the estimate of the increased risk. There are some limitations to the available data and the unpublished data is subject to ongoing evaluation, and therefore definitive conclusions cannot be reached. Non-clinical data regarding teratogenicity are inconclusive.

- Very limited data exist on the risk of neurodevelopmental outcomes and these are suggestive of no increased risk. However, longer-term follow-up data are not yet available from the most recent and largest unpublished study and this risk therefore currently remains unknown.

- The data available from clinical studies do not allow any firm conclusion to be drawn and the risk remains uncertain. Non-clinical data report on effects of pregabalin on fetal growth and development, but these effects were only seen at doses much higher than those used in humans.

3.9 Topiramate

Topiramate (Topamax) is indicated as monotherapy in adults, adolescents and children aged older than 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures. It is also indicated as adjunctive therapy in adults, adolescents and children older than 2 years of age with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.

NICE guidance recommends that topiramate can be used first line for myoclonic seizures and as adjunctive treatment in generalised tonic-clonic, myoclonic and focal seizures.

Congenital malformations

Data from meta-analyses (Weston et al, 2016 Risk Ratio 3.69 [95% CI 1.36-10.07] vs women without epilepsy and Risk Ratio 1.99 [95% CI 0.65- 6.08] vs women with epilepsy, Veroniki et al, 2017a Odds Ratio 1.90 [95% CrI 1.17, 2.97]) and larger epidemiological studies in pregnancy registries (Hernandez-Diaz et al, 2012 Relative Risk 3.8 [95% CI 1.4-10.6] vs women without epilepsy, Relative Risk 2.2 [95% CI 1.2-4.0] vs women with epilepsy) and national birth registers (Kallen et al, 2013 Relative Risk 3.73 [95% CI 1.97-8.11]) support an increased risk of major congenital malformations in children born to mothers who took topiramate during pregnancy compared with controls (unexposed women with or without epilepsy) and in comparison with mothers who took lamotrigine or levetiracetam but not those who took carbamazepine, phenobarbital or phenytoin. With regards to risk of specific malformations, the available data suggest an increased risk of oral cleft lip or palate, hypospadias and atrial septal defect in association with topiramate. While the evidence to support an increased risk of major congenital malformations is not consistent across all studies, those that do not suggest an increased risk tend to be studies with a smaller number of pregnancies exposed to topiramate.

In clinical studies where the effect of dose is examined, the findings are inconsistent. The meta-analysis by Weston et al, (2016) and data from the North American Antiepileptic Drug Pregnancy Registry and the Australian Pregnancy Registry failed to observe an increased risk of major congenital malformations with increasing doses of topiramate. Although a study in the UK Epilepsy and Pregnancy Registry (Hunt et al, 2008) and a study in a US healthcare database (US 2010 Medicaid Analytic eXtract) (Hernandez-Diaz et al, 2018) suggest a dose–dependent effect, only limited numbers of exposed pregnancies were involved in these analyses but these studies do provide some evidence of a dose effect.

Clinical studies examining the effect of polytherapy are more limited and are restricted to data from the UK Epilepsy and Pregnancy Registry and the Australian Pregnancy Registry, involving more than 300 exposed pregnancies. These data support an increased risk of congenital malformations following exposure to antiepileptic drug polytherapy regimens that include topiramate, and the Australian Pregnancy Registry data suggest that the increased risk observed with antiepileptic drug polytherapy is eliminated when pregnancies involving topiramate or valproate are excluded.

Overall, the data are supportive of a median prevalence of congenital malformations with topiramate of 4–5% and an increased risk compared with unexposed women with or without epilepsy.

In non-clinical studies, topiramate is reported to be teratogenic in rodents and rabbits at plasma concentrations relevant to human therapeutic doses.

Neurodevelopmental disorders and delay

There are extremely limited clinical data available to inform on the effect of topiramate exposure during pregnancy and the risk of neurodevelopmental disorders in the offspring. Data from a very small study by Rihtman et al, (2012), that involved only 9 children whose mothers had taken topiramate during pregnancy suggested that, compared with control children, topiramate had an adverse effect on cognitive, motor, and behavioural outcomes, as well as on IQ score, and motor and visual spatial skills. In contrast, a retrospective observational study in the UK Epilepsy and Pregnancy Registry (Bromley et al, 2016b) reported on data for 27 children who had prenatal exposure to topiramate and the findings did not suggest reductions in the cognitive abilities of the children. More recent data from a cross sectional study involving 25 women prospectively enrolled in the UK Epilepsy and Pregnancy Registry suggests the possibility of poorer development outcomes for children exposed to topiramate (communication, daily living and socialisation skills) and raises concerns about a higher incidence of autistic spectrum disorder in children exposed to topiramate compared with UK rates (Knight 2020). However, the number of exposures in the available clinical studies remains very limited and suggests that this is an area where further study would be very important.

Data from non-clinical studies in rats published in the scientific literature reported some evidence of neurodegenerative changes in the brains of the offspring exposed during pregnancy (Glier et al, 2004, Singh M, Mishra A., 2005, Hashish 2014). Limitations in the study designs, combined with conflicting findings in a Good Laboratory Practice compliant study in which there was no sign of degenerative changes in the brains of rat offspring means that there is no clear evidence of a potential for topiramate to adversely affect central nervous system development.

Other reproductive toxic effects on the fetus or neonate

Prevalence data from the North American Antiepileptic Drug Pregnancy Registry (Hernandez Diaz et al, 2017) as well as studies in Danish and Norwegian population birth registers (Killic et al, 2014, Veiby et al, 2014) indicate an approximate 2–3-fold increased prevalence of babies born small for their gestational age following topiramate in-utero exposure compared with unexposed pregnancies or in-utero lamotrigine exposure. These data are supported by the meta-analysis of Veroniki et al, 2017a. Two smaller epidemiological studies (Hunt et al, 2008 and Wade, 2015) did not show an increased relative risk of small for gestational age but these studies may not have been adequately powered to detect an increase in risk.

The available clinical data examining the effect of topiramate on fetal loss are very limited and the findings are inconsistent (Ornoy et al, 2008, Trivedi et al, 2018, Vajda et al, 2018, Veroniki et al, 2017a). The studies contain limited numbers of exposed pregnancies and for the studies that suggest an increased risk it is considered that the results may be affected by confounding. Similarly the available clinical data on the effects of topiramate on preterm birth are very limited; the meta-analysis by Veroniki et al, 2017a, a study in the North American Antiepileptic Drug Pregnancy Registry (Hernandez-Diaz et al, 2014) and a study by Ornoy et al, 2008 do not suggest an increased risk but given the limited data, no firm conclusions can be reached.

Non-clinical data report reduced fetal weights in offspring exposed to topiramate during pregnancy.

Key findings for topiramate

Overall the available clinical and non-clinical data support the following key findings for topiramate:

- A moderate amount of post-marketing data exist on the risk of birth abnormalities following the use of topiramate during pregnancy, with the available studies involving around 1,000 pregnancies exposed to topiramate in the first trimester. These data support that 4-5% of children exposed to topiramate monotherapy during pregnancy have congenital malformations and that this risk is increased compared with children of mothers who were not exposed to antiepileptics during pregnancy (2-3% in the general population) and possibly dose-dependent. In non-clinical studies topiramate is teratogenic in rodents and rabbits at human therapeutic doses.

- Very limited data exist on the risk of neurodevelopmental outcomes and, whilst there are some data indicative of adverse effects, overall this risk is uncertain.

- Clinical and non-clinical data support that the use of topiramate during pregnancy affects fetal growth and development, resulting in babies being more likely to be born with low birth weight and small for gestational age.

3.10 Zonisamide

Zonisamide (brand name Zonegran) is indicated for use as monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy and also for adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and older.

NICE guidance recommends that it may be considered for use by a tertiary epilepsy specialist when adjunctive treatment is not effective or not tolerated, and therefore its usage is limited. Prescription cost analysis data show that 164,243 prescription items for zonisamide were dispensed in England in 2019 and data from the CPRD suggest that its use in women of childbearing age is limited.

Congenital malformations

The available clinical data from the use of zonisamide in pregnant women remains extremely limited, with the largest data set (90 pregnancies exposed to zonisamide monotherapy) being that from a study in the North American Antiepileptic Drug Pregnancy Registry (Hernández-Díaz et al, 2012), which did not report any congenital malformations. Based on the pooled data from this study the prevalence of major malformations (any type) for children exposed to zonisamide was calculated to be 0.28% (95% CI 0.25–2.39) in the meta-analysis by Weston et al, 2016.

Further clinical data are available from a small retrospective questionnaire-based study conducted in Japan (Kondo et al, 1996) and the Swedish Medical Birth Register (Källén et al, 2013). The study by Kondo et al, reported on the outcomes of 26 pregnancies, of which only 4 were pregnancies exposed to zonisamide monotherapy. Congenital malformations were detected in 2 offspring (7.7%) exposed to zonisamide as part of polytherapy, so the role of zonisamide is unclear. In the study by Källén et al, there were only 7 pregnancies exposed to zonisamide, of which 3 were exposed to zonisamide monotherapy; no congenital malformations were reported in any of these pregnancies.

Overall, very few clinical studies have examined the risk of major congenital malformations in pregnancies exposed to zonisamide and the number of pregnancies exposed to monotherapy is very small (less than 100 pregnancies).

Zonisamide is reported to be teratogenic in multiple animal species, both rodent and non-rodent at plasma concentrations relevant to the human therapeutic dose.

The limited clinical data, coupled with the non-clinical data showing a teratogenic effect of zonisamide, mean that the risk of malformations with zonisamide use during pregnancy remains uncertain and the possibility of an increased risk of malformations can neither be confirmed nor ruled out. Any emerging data should be carefully evaluated to better inform the risk.

Neurodevelopmental disorders and delay

No clinical studies have examined the effect of exposure to zonisamide during pregnancy on the neurodevelopment of children.

The available non-clinical data are very limited and focus on an identified neuroprotective property of zonisamide in different settings, such as during ischaemic damage. To date there are no non-clinical studies reporting a developmental neurotoxic effect.

Other reproductive toxic effects on the fetus or neonate

Effects on fetal development and growth have also been observed in clinical studies. The largest data set from the North American Antiepileptic Drug Pregnancy Registry (Hernández-Díaz et al, 2014 and 2017) showed an increased risk of being small for gestational age and effects on birth weight and birth length. Hernández-Díaz (2017) reported a prevalence of 10.2% of babies small for gestational age in 125 pregnancies exposed to zonisamide and the same group in 2014 reported a similar prevalence of small for gestational age (12.2%) in 98 pregnancies exposed to zonisamide along with a significant effect on the mean birth weight (mean lower birth weight of 202 g) and mean birth length (mean lesser birth length of 1cm) compared with 1,581 pregnancies exposed to lamotrigine.

Non-clinical studies in several animal species have reported reduced fetal bodyweight gain and a reduction in growth parameters in the fetus as well as reductions in maternal bodyweight gain.

Key findings for zonisamide

Overall the available clinical and non-clinical data support the following key findings for zonisamide:

- Very limited clinical data exist on the risk of birth abnormalities following the use of zonisamide during pregnancy with the available studies only involving around 100 pregnancies exposed to zonisamide. The non-clinical data suggest that there is a possibility that exposure to zonisamide during pregnancy may be associated with an increased risk of birth abnormalities The risk remains uncertain and the possibility of an increased risk cannot be confirmed or ruled out.

- There are no clinical data and very limited non-clinical data on the risk of neurodevelopmental outcomes and this risk remains unknown.

- Use of zonisamide during pregnancy is associated with adverse effects on fetal growth and development. Studies involving around 100 pregnancies support that babies born to mothers exposed to zonisamide during pregnancy were more likely to be smaller than expected for their age compared with babies born to mothers who took another antiepileptic drug (lamotrigine) during pregnancy.

3.11 Other antiepileptic drugs

The section summarises the data and conclusions on the following antiepileptic medicines: brivaracetam, clobazam, clonazepam, eslicarbazepine, ethosuximide, lacosamide, rufinamide, perampanel, primidone, tiagabine and vigabatrin

For the majority of these drugs the data relating to safety of use during pregnancy remains limited or very limited. For perampanel, primidone and vigabatrin there are data on less than 300 exposed pregnancies and for brivaracetam, eslicarbazepine, ethosuximide, lacosamide, rufinamide, and tiagabine there are data on less than 100 exposed pregnancies. Given the limited data, no firm conclusions can be drawn with regards to the safety of use of these antiepileptic drugs during pregnancy and the risks remain unclear.

For both clobazam and clonazepam, there are data on approximately 300 and 1,000 exposed pregnancies respectively; however, this is still a relatively moderate number and the findings are inconsistent.

For clobazam, although there are some studies that are suggestive of an increased risk of major congenital malformations, the numbers of exposed pregnancies within the individual studies remain relatively small (the largest study includes data on 119 exposed pregnancies but other studies are much smaller) and the available data is not be considered to provide a robust basis on which to reach firm conclusions.

With regards to clonazepam, generally the data are not supportive of an increased risk of major congenital malformations; however, this finding is based on a limited number of studies. The individual studies generally include around 100 exposed pregnancies and are not sufficiently powered to rule out an increased risk. Subsequently, a conclusion cannot be reached with any certainty and the risk pertaining to congenital malformations remains unclear. Similarly, the data relating to effects on neurodevelopmental outcomes are

generally not suggestive of an increased risk. A study by Elkjaer et al, (2018) showed a detrimental effect on school performance, however, this effect was not consistently seen in all school performance tests and the absolute differences seen were small. Therefore, the data do not allow a firm conclusion to be reached on the adverse effect of clonazepam on neurodevelopmental outcomes and the possibility of adverse effects cannot be ruled out; any emerging data should be carefully evaluated. In relation to the risk of other reproductive toxicity effects, the data are generally not suggestive of adverse effects on fetal growth, however, there are conflicting data on the risk of fetal loss, with a study by Bech et al, (2018) suggesting that high dose clonazepam may be associated with an increased risk. However, the authors of this study highlight that they did not have information on the actual antiepileptic drug dose prescribed or taken nor did they know if the dose was changed during the pregnancy, which may limit the validity of the analyses on dose-response.

Overall, the available data do not allow for robust conclusions to be drawn on the safety of use during pregnancy of brivaracetam, clobazam, clonazepam, eslicarbazepine, ethosuximide, lacosamide, rufinamide, perampanel, primidone, tiagabine and vigabatrin etc and the risks remain uncertain; the possibility of adverse effects can neither be confirmed nor ruled out.

4 Key conclusions

The Commission on Human Medicines and its Expert Advisory Group on Neurology, Pain and Psychiatry, whose meetings were attended by representatives of patient groups and charities, have advised that these data support the following conclusions:

Lamotrigine and levetiracetam are the safer antiepileptics to use during pregnancy and overall the available data support:

- no increased risk of major congenital malformations or other reproductive toxic effects at the usual maintenance doses, based on a large amount of data for both drugs;
- for lamotrigine the data for an increased risk of major congenital malformations at higher doses are contradictory;
- with regards to the risk of neurodevelopmental disorders and delay, the data for both lamotrigine and levetiracetam are more limited. Although the limited available data did not suggest an increased risk for either antiepileptic drug, the limitations of the available data mean the possibility of an increased risk of neurodevelopmental disorders and delays cannot be ruled out.

For all other antiepileptics reviewed, with regards to the risk of major congenital malformations:

- use of **carbamazepine, phenobarbital, phenytoin and topiramate** during pregnancy is **associated with an increased risk of major congenital malformations** compared with that seen in the general population and unexposed women with epilepsy;
- the **increased risk seen with carbamazepine, phenobarbital and topiramate is dose-dependent** but no dose has been found to be without risk;
- pregabalin may be associated with a slightly increased risk of major congenital malformations but further data are needed to reach a definitive conclusion;
- the risks remain uncertain for gabapentin, oxcarbazepine, and zonisamide and the possibility of an increased risk can neither be confirmed nor ruled out;

In relation to the risk of neurodevelopmental disorders the available non-clinical and clinical data are limited but that which is available supports that:

- carbamazepine use during pregnancy does not appear to be associated with an increased risk of adverse effects on neurodevelopment and delay in humans; however, the non-clinical data showing some neurotoxic effects and this coupled with the limitations of the clinical data mean that an increased risk cannot be definitively ruled out;
- for **phenobarbital and phenytoin,** although the clinical studies report inconsistent findings, considering these alongside the non-clinical studies which demonstrate a possible effect, the **totality of the data support the possibility of adverse effects on neurodevelopment**;
- some recent data for topiramate raise concerns that its use during pregnancy may be associated with poorer development outcomes in the children exposed in utero, however, the numbers in the available studies remain limited and further data from larger studies are needed to reach firm conclusions in this respect.
- for gabapentin, oxcarbazepine, pregabalin, and zonisamide the data are either lacking or extremely limited and sometimes inconsistent, meaning that the risks remain uncertain and the possibility of an increased risk cannot be ruled out.

The available non-clinical and clinical data relating to the risk of other reproductive toxics effects supports that:

- use of **phenobarbital, topiramate, and zonisamide** during pregnancy is associated with an **increased risk of intrauterine growth retardation** (small for gestational age), where this is not currently reflected in product information updates are needed;
- non-clinical data for carbamazepine, gabapentin, oxcarbazepine, topiramate, and zonisamide show they can affect fetal growth but the clinical data are either too limited or report inconsistent findings. Overall the risks of other reproductive toxic effects with carbamazepine, gabapentin, oxcarbazepine, and pregabalin remain uncertain.

Overall, the available data do not allow for robust conclusions to be drawn on the safety of use during pregnancy of brivaracetam, clobazam, clonazepam, eslicarbazepine, ethosuximide, lacosamide, rufinamide, perampanel, primidone, tiagabine and vigabatrin. The risks of major congenital malformations, neurodevelopmental disorders and delay, and other reproductive toxic effects remain uncertain; the possibility of adverse effects can neither be confirmed nor ruled out.

Need for further data

The review has confirmed that for some of the AEDs that are frequently used, such as gabapentin, oxcarbazepine and zonisamide the data relating to safety of use during pregnancy remains limited or extremely limited and that further data are needed to more fully inform our understanding of the risks associated with their use during pregnancy.

Usage data for pregabalin and gabapentin clearly show that there is significant usage of both these products in women of childbearing potential and they are among the most commonly used antiepileptic drugs during pregnancy, however, it is recognised that the majority of such is used is likely to be in the pain and anxiety indications. For pregabalin, there are emerging unpublished clinical data which are currently undergoing further evaluation but are suggestive of a possible slight increase in overall risk of congenital malformations. For gabapentin, the Marketing Authorisation holder has recently been requested to perform a population-based cohort study examining pregnancy outcomes, which ideally will include a sufficient number of exposed pregnancies to better inform our understanding of the risks to the unborn baby. The findings of both of these studies along with any other emerging data on safety of use during pregnancy of any of the antiepileptic drugs will be carefully evaluated as they become available.

For topiramate, more recent data suggests the possibility of poorer development outcomes for children exposed during pregnancy and the possibility of a higher incidence of autistic spectrum disorder in children exposed to topiramate. The number of exposures in the available clinical studies remains very limited and this is an area where further study would be very important.

Table 1: Key conclusions for the individual AEDs for each of the risk areas reviewed.

The colour coding used within this table indicates the following:

data do not support an increased risk.

data support an increased risk.

data are considered more limited and inconsistent but overall supportive of an increased risk.

risks remain uncertain either due to the limited amount of data and/or the limitations of the available data.

	Congenital malformations	Neurodevelopmental disorders and delay	Other Reproductive toxic effects
Carbamazepine (CBZ)	Large amount of clinical data support an increased risk 2-3 fold higher than women without epilepsy ~9,000 exposed pregnancies (~6,000 1st trimester) Non-clinical data report teratogenic effects at human therapeutic doses	Large amount of clinical data do not support an increased risk Non-clinical data report neurodegenerative effects, but no neurobehavioural effects in the few studies performed	Large amount of clinical data – inconsistent findings ~3,500 exposed pregnancies Non-clinical data report adverse effects on fetal growth
Gabapentin (GBP)	Moderate amount of clinical data not suggestive of ↑risk ~600 1st trimester exposed pregnancies Non-clinical studies report inconsistent findings	Very limited clinical data Limited non-clinical studies report some neurodegenerative effects but the findings are unclear	Moderate amount of clinical data – inconsistent findings and studies often underpowered ~500 exposed pregnancies Non-clinical data report adverse effects on fetal growth
Lamotrigine (LMT)	Large amount of clinical data consistently support no increased risk >12,000 monotherapy exposed pregnancies Non-clinical data do not report a teratogenic effect at human therapeutic doses	Clinical data do not support an increased risk but limitations of the data mean an increased risk cannot be definitively excluded Non-clinical data report some neurobehavioural effects	Large amount of clinical data consistently support no increased risk ~3,000 exposed pregnancies Non-clinical data report effects on fetal weight but likely due to maternal toxicity
Levetiracetam (LEV)	Large amount of clinical data consistently support no increased risk ~1,800 exposed pregnancies (~1,500 1st trimester)	Clinical data do not support an increased risk but limitations of the data mean an increased risk cannot be definitively excluded	Limited clinical data but consistently support no increased risk ~200 exposed pregnancies
Oxcarbazepine (OXC)	Moderate amount of clinical data not suggestive of increased risk ~800 exposed pregnancies (~600 1st trimester) Non-clinical data report teratogenic effects at human therapeutic doses	Moderate amount of clinical data Non-clinical data are very limited but neurodegenerative effects have been reported	Moderate amount of clinical data – inconsistent findings ~800 exposed pregnancies Non-clinical data report adverse effects on fetal growth
Phenobarbital (PHB)	Clinical studies support an increased risk of Major Congenital Malformations ~1,800 exposed pregnancies (~600 1st trimester) Limited non-clinical data report a teratogenic effect	Inconsistent findings from clinical data Non-clinical data report adverse effects Overall data suggestive of the possibility of a detrimental effect	Studies support an increased risk of effects on fetal growth: small for gestational age but not low birth weight
Phenytoin (PHT)	Increased risk 2-3 fold higher than women without epilepsy >2,000 exposed pregnancies (~1,000 1st trimester) Non-clinical data report a teratogenic effect	Inconsistent findings from clinical data Non-clinical data report adverse effects Overall data suggestive of the possibility of a detrimental effect	Moderate amount of clinical data not suggestive of ↑risk >400 exposed pregnancies Non-clinical data report effects on fetal growth
Pregabalin (PGB)	Moderate amount of clinical data not suggestive of ↑risk ~600 1st trimester exposed pregnancies Non-clinical data regarding teratogenicity are inconclusive	Limited clinical data from one study with methodological limitations Non-clinical data report possible neurobehavioural effects	Moderate amount of clinical data not suggestive of ↑risk mainly from one study with methodological limitations >500 exposed pregnancies Non-clinical data do not report adverse effects on fetal weight
Topiramate (TPA)	Clinical studies support increased risk of Major Congenital Malformations that is ~3 fold higher than women without epilepsy ~1,000 1st trimester exposed pregnancies Non-clinical data report teratogenic effects at human therapeutic doses	Very limited data but some recent data are suggestive of an increased risk Non-clinical data have limitations and no firm conclusions can be drawn	Clinical studies support an increased risk of effects on fetal growth: increased risk of small for gestational age and low birth weight >500 exposed pregnancies Non-clinical data report adverse effects on fetal growth
Zonisamide (ZNS)	Very limited data – no conclusions can be drawn <100 monotherapy exposed pregnancies Non-clinical data report teratogenic effects at human therapeutic doses	No clinical data available Non-clinical data are very limited	Clinical studies support an increased risk of effects on fetal growth: increased risk of small for gestational age and low birth weight >200 exposed pregnancies Non-clinical data report adverse effects on fetal growth

5 Appendix 1

Table 1: Prevalence rate of Congenital Malformations for prioritised AEDs

	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Topiramate	Valproate	Zonisamide
Meta-analyses											
Veroniki et al, 2017a	4.14% 8437 exposures	2.43% 329 exposures	2.62% 6290 exposures	1.77% 1015 exposures	2.96% 372 exposures	**5.50%** **1709 exposures**	**6.08%** **2237 exposures**	-	**4.67%** **599 exposures**	**9.07%** **4455 exposures**	-
Weston et al, 2016	**3.71% (95% CI 3.19 to 4.27)** **4.93% (95% CI 3.84 to 6.16)** Random effects modelling* **RR 2.01 (1.20, 3.36)** vs WWOE **RR 1.50 (1.03, 2.19)** vs WWE 4666 exposures	1.47% (95% CI 0.26 to 3.64) RR 0.61 (0.07, 5.18) vs WWOE RR 1.50 (1.16, 0.23, 5.93) vs WWE 190 exposures	2.31% (95% CI 1.87 to 2.78) RR 1.68 (0.78, 3.65) vs WWOE RR 1.07 (.064, 1.77) vs WWE 4195 exposures	1.77% (95% CI 0.98 to 2.79) RR 2.16 (0.76, 6.17) vs WWOE RR 0.32 (0.10, 1.07) vs WWE 817 exposures	2.39% (95% CI 0.85 to 4.68) RR 1.94 (0.53, 7.15) vs WWOE RR 2.75 (0.53, 14.43) vs WWE 238 exposures	7.10% (95% CI 5.36 to 9.08)) **RR 2.84 (1,57, 5.13)** vs WWOE RR 1.95 (0.97, 3.93) vs WWE 709 exposures	**5.38%** **(95% CI 4.22 to 6.67)** **6.26%** **(95% CI 4.37 to 8.47)** Random effects modelling **RR 2.38 (1.12, 5.03)** vs WWOE **RR 2.40 (1,42, 4.08)** vs WWE 1279 exposures	-	4.28% (95 % CI 2.65-6.29) **RR 3.69 (1.36, 10.07)** vs WWOE RR 1.99 (0.65, 6.08) vs WWE 473 exposures	9.09% (95% CI 8.02 to 10.23) 10.93% (95% CI 8.91 to 13.13) Random effects modelling* **RR 5.69 (3.33, 9.73)** vs WWOE **RR 3.13 (2.16, 4.54)** vs WWE 2565 exposures	0.28% (95% CI 0.25 to 2.39) RR 0.44 (0.02, 7.93) vs WWOE 90 exposures
Meador et al, 2008	4.62% (95% CI 3.48 to 5.76) CBZ mono 7.10% (95% CI 3.71 to 10.49) CBZ dual 8.57 (95% CI 1.99 to 15.16) CBZ poly 4411 mono 942 dual and 70 poly exposures	-	2.91% (95% CI 2.00 to 3.82) LMT mono 5.59% (95% CI 1.11 to 10.08) LMT dual 1337 mono and 599 dual exposures	-	-	4.91% (95% CI 3.22 to 6.59) PHB mono **9.19% (95% CI 5.88 to 12.50) PHB dual** **14.57% (95% CI 8.81 to 20.33) PHB poly** **945 PHB mono exposures**	7.36% (95% CI 3.60 to 11.11) PHT mono **11.47%** **(95% CI 6.65 to 16.30)** **PHT dual** **14.27%** **(95% CI 8.95 to 19.60)** **PHT poly** 1198 mono 720 dual and 276 poly exposures	-	-	**10.73%** **(95% CI 8.16 to 13.29)** **VPA mono** **9.79%** **(95% CI 7.57 to 12.02)** **VPA dual** **25.00%** **(95% CI 5.97 to 44.03)** **VPA poly** 2097 mono 694 dual and 20 poly exposures	-
Pregnancy Registries											
UK and Ireland Pregnancy Registry (UKEPR)											
UKEPR ǂ Campbell et al, 2014	2.6% (95% CI 1.9 to 3.5) 1657 exposures		2.3% (95% CI 1.8 to 3.1) 2098 exposures							6.7% (95% CI 5.5 to 8.3) 1220 VPA exposures	
ǂ UKEPR Morrow et al, 2006	2.2% (95% CI 1.4 to 3.4) 927 exposures	3.2% (95% CI 0.6 to 16.2) 31 exposures	3.2% (95% 2.1 to 4.9) 647 exposures	0.0% (95% CI 0.0 to 14.9) 26 exposures			3.7% (95% CI 1.3 to 10.2) 82 exposures		7.1% (95% CI 2.0-22.6) 28 exposures	6.2% (95% CI 4.6 to 8.2) 762 exposures	
ǂ Hunt et al, 2008									4.8% (95% CI 5.6-14.1) 70 TPM mono exposures		
European Pregnancy Registry (EURAP)											
Tomson et al, 2018	**5.5%** **(95% CI 4.5 to 6.6)** 1957 exposures		2.9% (95% CI 2.3 to 3.7) 2154 exposures	2.8% (95% CI 1.7 to 4.5) 599 exposures	3.0% (95% CI 1.4 to 5.4) 333 exposures	**6.5%** **(95% CI 4.2 to 9.9)** 294 exposures	6.4% (95% CI 2.8 to 12.2) 125 exposures		3.90% (95% CI 1.5-8.4) 152 exposures	**10.3%** **(95% CI 8.8 to 12.0** 1381exposures	
North American Antiepileptic Drug Pregnancy Registry (NAAEDPR)											
Published on NAAEDPR website - 2019	2.9% (95% CI 2.0 to 4.0%) 1110 exposures	1.5% (95% CI 0.37 to 3.9) 207 exposures	2.3% (95% CI 1.7 to 2.9) 2179 exposures	2.3% (95% CI 1.5 to 3.4) 1029 exposures	1.9% (95 % CI 0.7 to 4.1%) 265 exposures	5.6% (95% CI 3.0 to 9.6%) 195 exposures	2.6% (95% CI 1.4 to 4.4) 431 exposures	-	5.1% (95% CI 3.4 to 7.4) 489 exposures	9.3% (95% CI 6.5 to 12.7%) 335 exposures	1.2% (95% CI 0.2 to 3.9%) 166 exposures
ǂ Hernandez-Diaz et al, 2012	**3.0%** (**95% CI 2.1 to 4.2)** 1033 exposures	0.7% (95% 0.02 to 3.8) 145 exposures	2.0% (95% CI 1.4 to 2.8) 1562 exposures	2.4% (95% CI 1.2 to 4.3) 450 exposures	2.2% (95% CI 0.6 to 5.5) 182 exposures	**5.5%** **(95% CI 2.8 to 9.7)** 199 exposures	2.9% (95% CI 1.5 to 5.0) 416 exposures		**4.2%** **(95% CI 2.4 to 6.8)** 359 exposures	**9.3%** **(6.4 to 13.0** 323 exposures	0 malformations 90 exposures
Australian Pregnancy Registry (APR)											
Vajda et al, 2019	5.9% 409 exposures		4.9% 406 exposures	3.6% 139 exposures	5.3% 19 exposures		2.3% 44 exposures		1.9% 53 exposures	**14.8%** **290 exposures**	
ǂ Vajda et al, 2014	5.5% 346 exposure		4.6% 307 exposures	2.4% 82 exposures	5.9% 17 exposures		2.4% 41 exposures		2.4% 42 exposures	**13.8%** **253 exposures**	
Prospective studies											
Patorno et al, 2017 Prospective cohort study								5.9% 477 exposures			
Petersen et al, 2017	3.29% (95% CI 1.66 to 5.82) 334 exposures		2.8% (95% CI 1.35 to 5.09) 357 exposures							6.55% (95% CI 3.71 to 10.57) 229 exposures	
Winterfeld et al, 2016 Prospective cohort study								**9.6%** 164 total 116 1st trimester (19 mono)			
ǂ Veiby et al, 2014ǂ	2.9% 685 exposures		3.4% 833 exposures	1.7% 118 exposures	1.8% 57 exposures	7.4% 27 exposures		3.3% 30 exposures	4.2% 48 exposures	**6.3%** **333 exposures**	
ǂ Fujii et al, 2013		4.1% 223 exposures									
ǂ Kallen et al, 2013	3.40% 1706 total and 1511 mono exposures	1.40% 143 total and 119 mono exposures	2.77% 1337 total and 1084 mono exposures	0.66% 151 total 57 mono exposures	6.90% 58 total and 40 mono exposures	7.14% 28 total and 17 mono exposures	6.94% 173 total and 140 mono exposures	1.56% 128 total and 111 mono exposures	**5.88%** **102 total and 49 mono exposures**	**7.19%** **862 total and 697 mono exposures**	14.28% 7 total and 3 mono exposures
ǂ Kaaja et al, 2003	3.96% 363 exposures				11% 9 exposures	4.54% 5 exposures	3.3% 124 exposures			**6.35%** **61 exposures**	

*Conducted due to significant variance

ǂ These studies were included in the Weston et al, 2016 and/or the Veroniki et al, 2017a meta-analyses and therefore for the purposes of the public assessment report these data will not be presented separately.

6 Appendix 2

Table 2: Effects on Cognitive function and risk of neurodevelopmental disorders for prioritised AEDs

Table 2a: Effects on IQ/Cognitive Effects

IQ/ Cognitive Effects								
	Carbamazepine	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Topiramate**	**Valproate**
Meta-analyses								
Veroniki et al, 2017b Cognitive Developmental Delay	OR 2.07 (0.82, 5.48) N=238	OR 0.93 (0.09, 5.10) N=43	OR 3.42 (0.65, 16.40)	-	OR 1.36 (0.18, 7.02) N=12	OR 2.55 (0.72, 8.55) N=111	**OR 3.14 (0.45, 16.53)** **N=**	**OR 7.40 (3.00, 18.46)** **N=**
Bromley et al, 2014 IQ mean (SD) Verbal IQ (VIQ) Performance IQ (PIQ)	IQ MD -0.03 (95% CI –3.08 to 3.01) Vs WWOE N=150 MD 1.84 (95% CI -2.13 to 5.80) Vs WWE N=163 Vs general population controls VIQ MD -1.81 (95% CI -4.94 to 1.33 PIQ MD 1.27 (95% CI -1.55 to 4.09) N=136	IQ mean 105.56, SD 12.49 versus control mean 108.71, SD 10.20, P>0.05 N=41 Verbal IQ and Performance IQ also did not significantly differ to control population	-	-	86.2 (SD 11) vs WWOE 93 (SD 14.4) N=41	PHT (n=29) mean 90.3 (95% CI 77 to 103) vs WWE control (n=32) mean 92.3 (95% CI 81 to 103) NS* Cognitive dysfunction OR 1.37 (95% CI 0.38 to 5.0) PHT (n=12)	**mean 96.33 SD 10.37)** **Vs WWOE** **mean 111.39 (SD 12.20), P=0.005** **N=9**	**MD-8.94 (-11.96, -5.92), P<0.00001, I^2=88%** **Vs WWOE** **N=76** **MD-8.17 (-12.80, -3.55), P=0.005, I^2=27%** **Vs WWE** **VIQ** **MD-11.39 (-14.68, -8.10), P<0.00001, I^2=0% vs general population** **N=64** **PIQ** **MD-10.48 (-13.94, -7.02), P<0.00001, I^2=68%** **N=64**
Banach et al, 2010 Wechsler Scale PIQ Bayley or McCarthy scale FSIQ	Wechsler scale Statistically significantly lower PIQ in CBZ (p<0.002) compared all control group; No statistically significant difference for either VIQ or FSIQ compared to all control group N=151 Bayley or McCarthy scales FSIQ no statistically significant different; CBZ vs control group (98 vs 102, p=0.3) N=83							
Pregnancy Registries								
Gopinath et al. 2015 Wechsler scale Full Scale IQ Mean (SD)	CBZ mono (40) 82.2 (13.9) vs 80.2 (13.4); p=0.449 CBZ all (76) 77 (15.2) vs 78.5 (1.4); p=0.466	LMT mono (1) 89 vs 80.8 (13.6); p=0.551 LMT all (4) mean 71.3 (17.9) vs 78.1 (14.6); p=0.356			**PB mono (n=22)** **74.5 (14)** **vs** **82.5 (13);** **p=0.013** PB all (n=59) 73.5 (14.4) vs 80 (14.4); p=0.05	PHT mono (n=11) 82.6 (13.5) vs 80.7 (13.7); p=0.656 PHT all (n=39) 74.9 (14.8) vs 78.7 (14.5); p=0.153	-	VPA mono (36) 82.8 (12.4) vs 77 (15.3); p=0.190 VPA all (53) 80.2 (12.7) vs 77 (15.3); p=0.313
Huber-Mollema et al2020 Wechsler Intelligence Scale Full-Scale IQ (FSIQ) Verbal IQ (VIQ) Performance IQ (PIQ) Processing Speed Index Mean (SD) Individual AED Vs VPA	FSIQ 105.3 (13.7) B 5.6 (SE 3.9) (95% -2.2 to 13.4), P=0.157 **VIQ** **106.2 (14.2)** **B 9.1 (SE 4.0) (95% 1.3 to 17.0), P=0.023** PIQ 102.8 (15.5) B 0.1 (SE 4.3) (95% -8.3 to 8.6), P=0.973 PSI 108.7 (12.1) B 5.1 (SE 4.2) (95% -3.3 to 13.5), P=0.229 N=32	**FSIQ** **109.2 (15.0)** **B 7.5 (SE 3.5) (95% 0.6 to 14.4), P=0.033** **VIQ** **109.7 (15.7)** **B 10.3 (SE 3.5) (95% 3.4 to 17.3), P=0.004** PIQ 106.0 (14.9) B 2.3 (SE 3.8) (95% -5.3 to 9.8), P=0.551 PSI 111.0 (14.4) B 6.3 (SE 3.8) (95% -1.1 to 13.7), P=0.097 N=82	FSIQ 110.8 (14.8) B 7.7 (SE 4.1) (95% --0.4 to 15.8), P=0.064 **VIQ** **114.0 (13.1)** **B 13.4 (SE 4.2) (95% 5.2 to 21.6), P=0.002** PIQ 104.4 (14.8) B -0.6 (SE 4.5) (95% -9.5 to 8.3), P=0.901 PSI 111.2 (16.2) B 4.9 (SE 4.4) (95% -3.9 to 3.6), P=0.275 N=25					FSIQ 103.2 (14.8) VIQ 100.6 (14.9) PIQ 105.3 (17.0) PSI 107.4 (18.6) N=22
Kerala Pregnancy Registry								
Thomas et al, 2007 Full Scale IQ (FSIQ-adaptation of Wechsler Intelligence Scale) Malayalam Language Test (MLT) – local proficiency test for language vs Age Matched Controls	FSIQ 83.6 (30.0); p=0.22 (all) 91.9 (21.7); p=0.86 (mono) MLT 71.5 (22.4); p=0.44 (all) 74.9 (21.0); p=0.87 (mono) N=28 (all) N=14 (mono)	-	-	-	FSIQ 84.9 (20.1); p=0.35 (all) **86.2 (11.0);** **p=0.07 (mono)** MLT 71.8 (14.9); p=0.47 (all) 70.6 (8.5); p=0.146 (mono) N=32 (all) N=14 (mono)	FSIQ 87.6 (19.0); p=0.96 (all) 97.8 (9.9) p=0.43 (mono) MLT 71.1 (15.7); p=0.51 (all) 76.0 (10.7); p=0.92 (mono) N=18 (all) N=5 (mono)	-	FSIQ 87.2 (29.8); p=0.90 (all) 98.5 (13.5); p=0.12 (mono) MLT 73.7 (21.1); p=0.95 (all) 81.5 (11.9); p=0.09 (mono) 19 VPA (all) 12 VPA (mono)

Prospective studies								
Cohen et al, 2019 Standardised mean of 6 years IQ (95% CI) Attention/concentration Verbal immediate Verbal delayed Delayed recognition Visual immediate Visual delayed Learning	**IQ** **106.2 (95% CI 103.1 to 109.3);** **Effect -5.4 (-10.4 to -0.4); p=0.0370** Attention/concentration 101.2 (96.8, 105.5) Effect -3.1 (-8.7, 2.6) Verbal immediate 103.2 (99.4, 107) Effect -1.6 (-6.5, 3.3) Verbal delayed 103.8 (99.5, 108.1) Effect 0 (-5.6, 5.5) Delayed recognition 101.5 (97.8, 105.2) Effect -3.8 (-8.6, 1) Visual immediate 98.6 (95, 102.1) Effect -3.1 (-7.7, 1.5) Visual delayed 103.4 (99.7, 107) Effect 0.2 (-4.5, 4.9) **Learning** **98.4 (94.6, 102.1)** **Effect-5.1 (-10, -0.3)** N=61	IQ 108.4 (95% CI 105.5 to 111.3); Effect -3.2 (-8.1 to -1.8); p=0.2111 **Attention/concentration** **98.2 (94.2, 102.3)** **Effect -6 (-11.5, -0.5)** Verbal immediate 103.1 (99.6, 106.7) Effect -1.7 (-6.5, 3.1) Verbal delayed 103.6 (99.6, 107.6) Effect -0.3 (-5.6, 5.1) Delayed recognition 103.1 (99.7, 106.6) Effect -2.2 (-6.8, 2.5) Visual immediate 100.6 (97.3, 103.9) Effect -1.1 (-5.6, 3.4) Visual delayed 105.3 (101.9, 108.7) Effect -2.2 (-2.4, 6.7) **Learning** **98 (94.5, 101.5)** **Effect-5.5 (-10.2, -0.8)** N=73	-	-	-	IQ 107.4 (95% CI 103.3 to 111.4); Effect -4.2 (-9.8 to 1.4); p=0.1467 Attention/concentration 98 (92.5, 103.6) Effect -6.2 (-12.7, 0.3) Verbal immediate 100.8 (96, 105.6) Effect -4 (-9.7, 1.6) Verbal delayed 99.1 (93.7, 104.5) Effect -4.8 (-11.1, 1.6) **Delayed recognition** **99.3 (94.6, 103.9)** **Effect -6 (-11.5, -0.5)** Visual immediate 97.3 (92.8, 101.8) Effect -4.4 (-9.7, 0.9) Visual delayed 99.4 (94.8, 104.1) Effect -3.7 (-9.1, 1.7) **Learning** **94.7 (89.9, 99.4)** **Effect-8.8 (-14.4, -3.3)** N=39	-	**IQ** **100.8 (95% CI 97.2 to 104.3);** **Effect -10.8 (-16 to -5.6); p<0.0001** **Attention/concentration** **94.1 (89.1, 99.1)** **Effect -10.2 (-16.3, -4.1)** **Verbal immediate** **94.5 (90, 98.9)** **Effect -10.4 (-15.8, -5.0)** **Verbal delayed** **92.2 (87.2, 97.3)** **Effect -11.6 (-17.7, -5.5)** **Delayed recognition** **90.4 (86, 94.7)** **Effect -14.9 (-20.2, -9.6)** **Visual immediate** **94.4 (90.3, 98.5)** **Effect -7.3 (-12.3, -2.2)** **Visual delayed** **95.2 (90.9, 99.4)** **Effect -8 (-13.2, -2.8)** **Learning** **90.2 (85.9, 94.6)** **Effect-13.3 (-18.6, -8)** **N=48**
Titze et al, 2008 Wechsler Adult Intelligence Scale (WAIS)					**adjusted total IQ: 98.0 SD11.9 versus control 105.4 SD11.0, p=0.037** **N=14 (3 mono)**			
Scolnik et al, 1994 Global IQ (Bayley or McCarthy Scale) Mean (SE) AED Vs Control	Global IQ 111.5 (19.7) Vs 114.9 (13.3) NS Reynell verbal comprehension 0.72 (1.4) Vs 1.05 (0.81) NS					**Global IQ** **103.1 (25.2)** **Vs 113.4 (13.1)** **Significant difference -10.6 (27.9)** **Reynell verbal comprehension** **0.2 (1.6)** **Vs 1.1 (0.95)** **Significant difference -0.47 (1.2)**		
Others								
Reinisch et al, 1995 Retrospective cohort study Denmark Wechsler Adult Intelligence Scale (WAIS) Verbal IQ (VIQ) Mean (SD) Danish Military Board Intelligence Test BPP scores (IBPP)	-	-	-	-	**WAIS** **VIQ 100.69 (14.94)** **Vs predicted 107.86 (6.38) equal to -7.17 (adjusted SE, 3.99; adjusted t, -1.79; df, 37; P<.04)** **IBPP** **mean difference -4.77;** **adjusted SE, 1.63; adjusted t, -2.92; df, 85; P<.002).**	-	-	- -
Hanson et al, 1976 WISC full scale IQ at 7 years Mean (SD)						**PHT** **91.7 (17.29)** **Vs** **Control** **96.83 (15.5); t=2,01, p<0.05** **N=83**		
Rihtman et al Israeli Teratogen Information Service IQ tests							Fluid reasoning (p=0.005) Quantitative reasoning (p=0.002) Visual-spatial (p=0.003) Verbal IQ (p=0.017), non-verbal IQ (=0.011) General IQ (p=0.005) 9 TPM exposures	

Table 2b: Effects on Developmental Quotient (DQ)

DQ/ Effects on development							
	Carbamazepine	**Lamotrigine**	**Levetiracetam**	**Phenobarbital**	**Phenytoin**	**Topiramate**	**Valproate**
Meta-analyses							
Veroniki et al, 2017b Language Delay (LD) Psychomotor developmental delay (PDD)	LD OR 4.32 (0.81, 26.93) N=117 PDD OR 1.68 (0.85, 3.41) N=249	LD OR 4.36 (0.68,25.41) N=59 PDD OR1.86 (0.72, 4.76) N=745	PDD OR 0.27 (0.00,4.26)	LD OR 1.06 (0.22,5.08) N=41 PDD OR 0.96 (0.39, 2.29) N=117	PDD OR 2.84 (0.97,7.93) N=83	PDD OR 3.89 (0.41,24.27) N=	**LD** **OR 7.95 (1.50,49.13)** **N=** **PDD** **OR 4.16 (2.04, 8.75)** **N=**
Bromley et 2014 DQ Mean	DQ **MD -5.58 (95% CI -10.83 to -0.34) Vs WWOE** **N=50** **MD -7.22 (95% CI -12.76 to -1.67 Vs WWE** **N=163**	Mean 99 (95% CI 94 to 103) vs general population mean 98.8 (95% CI 96 to 102); P=0.62 N=51	Mean 99.9 (95% CI 97 to 103,) vs WWOE mean 100 (95% CI 99 to 102); P=0.21 N=34 Mean 99 (95% CI 94 to 103,) vs WWE mean 104 (95% CI 101 to 108); P=0.21 N=34	mean 115 (SD not reported) vs general population mean 119 (SD not reported) P=0.372 Mean 90.3 (94, 97) Vs WWE Mean 92.3 (81, 103) N=41	MD -0.12 (95% CI -7.54 to 7.30, P=0.98) vs general population N=20 Mean 90.3 (77, 103) Vs WWE Mean 92.3 (81,103) N=29 Motor development PHT (n=15) mean 98 versus control mean 106 (CIs unclear)	-	**mean 92 (87, 96)** **Vs WWOE** **mean 100 (99, 102);** **P<0.001** **N=42** **Bayley Scales** **MD -8.72 (-14.31, -3.31),** **P=0.002, I^2=0%** **N=123** **Griffiths Mental Development Scale** **mean 92 (87, 96)** **Vs WWE** **mean 104 (101, 108)**
Pregnancy Registries							
Cummings et al, 2011 Bayley Scale of Infant Development Griffiths Mental Development Scale	20.4% evidence of mild or significant developmental delay **CBZ vs control** **Adjusted OR 7.7 (95% 1.4 to 43.1); p<0.01** 49 exposures	2.9% evidence of mild or significant developmental delay LMT vs control Adjusted OR 1.1 (95% 0.1 to 13.7); p<0.01 35 exposure					39.6% evidence of mild or significant developmental delay **VPA vs control** **Adjusted OR 26.1 (95% 4.9 to 139); p<0.001** **58 exposures**
Shallcross et al, 2011 Griffiths Mental Development Scale Mean (95% CI) Overall DQ Locomotor Personal and Social Hearing and Language Hand and Eye Coordination Performance Overall DQ OR AED vs Control			Overall DQ 99.96 (95% CI 97.16 to 102.76) Locomotor 97.35 (95% CI 93.66 to 98.29) Personal and Social 98.00 (95% CI 93.73 to 102.27) Hearing and Language 100.57 (95% CI 96.89 to 104.24) Hand and Eye Coordination 101.88 (95% CI 97.46 to 106.30) Performance 101.75 (95% CI 98.02 to 105.47) N=51				**Overall DQ** **87.63 (95% CI 82.68 to 93.18)** Locomotor 84.66 (95% CI 78.72 to 90.59) Personal and Social 89.82 (95% CI 83.62 to 96.02) Hearing and Language 90.48 (95% CI 84.29 to 96.66) **Hand and Eye Coordination** **88.21 (95% CI 82.07 to 94.35)** **Performance** **88.88 (95% CI 83.29 to 94.48)**
Birth Registers							
Wide et al, 2002 Griffiths Mental Development Scale Mean (95% CI for the differences of mean score) Total Score Locomotor function Personal and Social Hearing and Language Hand and Eye Coordination Performance Overall DQ	Locomotor function 104 (95% CI -5.1 to 4.7) Personal and Social behaviour 107 (-3.4 to 3.3) Hearing and Speech 105 (-9.6 to 6.7) Hand and Eye Coordination 100 (-6.1 to 3.5) Performance 105 (-8.0 to 2.5) Practical reasoning 101 (-11.1 to 3.1) Total Score 618 (-34.7 to 11.8) N=35				**Locomotor** **98 (95% CI -14.0 to -0.4)** Personal and Social Behaviour 105 (95% CI -8.2 to 2.5) Hearing and speech 111 (95% CI -11.9 to 10.4) Hand and Eye Coordination 101 (95% CI -7.8 to 5.4) Performance 110 (95% CI -8.4 to 11.2) Practical reasoning 97 (-23.0 to 3.5) Total Score 612 (-66.8 to 19.7) N=15	-	
Prospective studies							
Cohen et al, 2019 Standardised mean of 6 years IQ (95% CI)	**IQ** **106.2 (95% CI 103.1 to 109.3);** **Effect -5.4 (-10.4 to -0.4); p=0.0370** Attention/concentration 101.2 (96.8, 105.5) Effect -3.1 (-8.7, 2.6) Verbal immediate 103.2 (99.4, 107) Effect -1.6 (-6.5, 3.3) Verbal delayed 103.8 (99.5, 108.1) Effect 0 (-5.6, 5.5) Delayed recognition 101.5 (97.8, 105.2) Effect -3.8 (-8.6, 1)	IQ 108.4 (95% CI 105.5 to 111.3); Effect -3.2 (-8.1 to -1.8); p=0.2111 **Attention/concentration** **98.2 (94.2, 102.3)** **Effect -6 (-11.5, -0.5)** Verbal immediate 103.1 (99.6, 106.7) Effect -1.7 (-6.5, 3.1) Verbal delayed 103.6 (99.6, 107.6) Effect -0.3 (-5.6, 5.1) Delayed recognition 103.1 (99.7, 106.6) Effect -2.2 (-6.8, 2.5)	-	-	IQ 107.4 (95% CI 103.3 to 111.4); Effect -4.2 (-9.8 to 1.4); p=0.1467 Attention/concentration 98 (92.5, 103.6) Effect -6.2 (-12.7, 0.3) Verbal immediate 100.8 (96, 105.6) Effect -4 (-9.7, 1.6) Verbal delayed 99.1 (93.7, 104.5) Effect -4.8 (-11.1, 1.6) **Delayed recognition** **99.3 (94.6, 103.9)** **Effect -6 (-11.5, -0.5)**	-	**IQ** **100.8 (95% CI 97.2 to 104.3);** **Effect -10.8 (-16 to -5.6);** **p<0.0001** **Attention/concentration** **94.1 (89.1, 99.1)** **Effect -10.2 (-16.3, -4.1)** **Verbal immediate** **94.5 (90, 98.9)** **Effect -10.4 (-15.8, -5.0)** **Verbal delayed** **92.2 (87.2, 97.3)** **Effect -11.6 (-17.7, -5.5)** **Delayed recognition** **90.4 (86, 94.7)** **Effect -14.9 (-20.2, -9.6)**

	Visual immediate 98.6 (95, 102.1) Effect -3.1 (-7.7, 1.5) Visual delayed 103.4 (99.7, 107) Effect 0.2 (-4.5, 4.9) **Learning** **98.4 (94.6, 102.1)** **Effect-5.1 (-10, -0.3)** N=61	Visual immediate 100.6 (97.3, 103.9) Effect -1.1 (-5.6, 3.4) Visual delayed 105.3 (101.9, 108.7) Effect -2.2 (-2.4, 6.7) **Learning** **98 (94.5, 101.5)** **Effect-5.5 (-10.2, -0.8)** N=73			Visual immediate 97.3 (92.8, 101.8) Effect -4.4 (-9.7, 0.9) Visual delayed 99.4 (94.8, 104.1) Effect -3.7 (-9.1, 1.7) **Learning** **94.7 (89.9, 99.4)** **Effect-8.8 (-14.4, -3.3)** N=39		**Visual immediate** **94.4 (90.3, 98.5)** **Effect -7.3 (-12.3, -2.2)** **Visual delayed** **95.2 (90.9, 99.4)** **Effect -8 (-13.2, -2.8)** **Learning** **90.2 (85.9, 94.6)** **Effect-13.3 (-18.6, -8)** **N=48**
Dean et al, 2002 Developmental delay (DD) Behaviour disorder (BD) N(%)	**DD 15 (22%);** **p<0.05** **BD 10 (14.5%);** **p<0.05** **N=70**	-	-	DD 6 (10%) BD 4 (6.6%) N=25	**DD 8 (33%);** **p<0.05** BD 1 (4.2%) **N=25**		**DD 13 (28%);** **p<0.05** **BD 5 (10.9%);** **p<0.05** **N=47**
Others							
Shankaran et al, 2001 Antenatal exposure to PHB or placebo between 24 to 32 weeks Bayley Scale of development In infant at 18-22 months Mental Development Index (MDI) Psychomotor Development Index (PDI) median (range)				MDI PHB 85 (49-124) Vs Placebo 86 (49-129) PDI PHB 91 (49-121) Vs Placebo 91 (49-134) N=344			

Table 2c: Autistic spectrum disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD)

Autistic disorders and Attention Deficit Hyperactivity disorder							
	Carbamazepine	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Valproate**
Meta-analyses							
Veroniki et al, 2017b Autism/dyspraxia (A/D) ADHD Vs WWE (untreated)	A/D OR 5.76 (95% CI 0.76 to 73.43) N=182 ADHD OR 2.32 (95% CI 0. 70 to 7.86) N=182	**A/D** **OR 8.88** **(95% CI 1.28 to 112.00)** **N=126** ADHD OR 1.63 (95% CI 0.41 to 6.06) N=105	A/D OR 3.64 (95% CI 0.00 to 222.30) LEV mono	**A/D** **OR 13.51** **(95% CI 1.28 to 221.40)** **OXC mono N=321**	ADHD OR 1.29 (95% CI 0.25,6.21) N=61	A/D OR 7.09 (95% CI 0.02 to 397.70) N=83 ADHD OR 0.63 (95% CI 0.07 to 4.07 N=41	**A/D** **OR 17.29** **(95% CI 2.40 to 217.60)** ADHD OR 2.84 (95% CI 0.82 to 9.99)
Bromley et al, 2014 ASD	Autistic traits (parental rating) OR 3.3 (0.5, 24.8 18 months) OR 2.5 (0.3, 19.1) 36 months N=41	Autistic traits (parental rating) OR 1.5 (0.2, 11.0) 18 months) **OR 5.0 (1.7, 14.4) 36 months** **N=154**	-	**-**	-	-	Autistic traits (parental rating) VPA 0% vs 0.5% control 18 months OR 3.7 (0.5, 28.4) 36 months N=19
Pregnancy Registries							
APR							
Wood et al, 2016 Autism traits (assessed using Childhood Autism Rating Scale)	Elevated CARs score 5.9% N=34	-	-	-			Elevated CARs score 7.7% N=26 (mono) **46.7%** **N=15 (poly)**
Huber-Mollema et a 2019 ASD ADHD diagnosis vs population norms	ADHD 2.8% vs 4.3% p=0.653; ASD 0% vs 1.5% p=0.453 N=37	ADHD 5.7% vs 4.3% p=0.529; **ASD 4.6% vs 1.5% p=0.02** N=88	ADHD 7.1% vs 4.3% p=0.897; ASD 3.6% vs 1.5% p=0.352 N=30				ADHD 3.8% vs 4.3%; p=0.897; **ASD 7.1% vs 1.5%;** **p<0.01** **N=26**
Birth Registers							
Veiby et al, 2013 Risk at 36 months Autistic traits (Social Communication Questionnaire) ADHD symptoms Vs children born to WWOE	Autistic traits 3.4% Vs 1.5% OR 2.5 (95% CI 0.3 to 19.1) ADHD symptoms 6.5% Vs 4.0% OR 2.0 (95% CI 0.5 to 8.6) N=31	**Autistic traits** **9.3% Vs 1.5%** **OR 5.0 (95% CI 1.7 to 14.4)** ADHD symptoms 7.0% Vs 4.0% OR 1.5 (95% CI 0.4 to 4.8) N=44	-	-	-	-	Autistic traits 5.6% Vs 1.5% OR 3.7 (95% CI 0.5 to 28.4) ADHD symptoms 5.6% Vs 4.0% OR 1.3 (95% CI 0.2 to 9.9) N=19
Others							
Christensen et al, 2019 ADHD Diagnosis Vs unexposed	7.33% 5.6 (95% CI 3.9 to 7.9) Incidence/1000 PYs aHR 1.23 (95% 0.84 to 1.82) N=423	2.96% 3.4 (95% CI 2.5 to 4.6) Incidence/1000 PYs aHR 0.84 (95% 0.59 to 1.19) N=1383		6.72% 5.5 (95% CI 3.7 to 8.1) Incidence/1000 PYs aHR 1.10 (95% 0.72 to 1.67) N=372			**8.82%** **7.2 (95% CI 5.2 to 9.8)** **Incidence/1000 PYs** **aHR 1.52 (95% 1.05 to 2.19)** **N=431**
Christensen et al, 2013 Autism Spectrum disorder (ASD) Childhood Autism Vs unexposed	ASD 1.04% aHR 1.0 (95% CI 0.4 to 2.8) Childhood Autism 0.52% aHR 1.4 (95% CI 0.4 to 2.8) N=386	- ASD 1.23% aHR 1.7 (95% CI 0.5 to 5.2) Childhood Autism 0.62% aHR 1.7 (95% CI 0.8 to 3.5) N=647	-	ASD 2.18% aHR 2.1 (95% CI 0.96 to 4.6) Childhood Autism 0.31% aHR 1.0 (95% CI 0.1 to 6.9) N=321	-	-	**ASD** **3.09%** **aHR 3.0 (95% CI 1.7 to 5.4)** **Childhood Autism** **1.80%** **aHR 4.9 (95% CI 2.3 to 10.3)** **N=388**

Table 2d: Other Neurodevelopmental Effects

Other Neurodevelopmental Effects									
	Carbamazepine	**Gabapentin**	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Topiramate**	**Valproate**
Pregnancy Registries									
Deshmukh et al, 2016 Vineland-II Adaptive Behaviour Scale Frequency of low and moderately low adaptive levels (%): Overall ABC domain Communication Daily Living Skills Socialization Motor Skills	**ABC** 5.1% CBZ vs LMT OR 1.46 (95% CI 0.24 to 9.03) **CBZ vs VPA** **OR 0.16** **(95% CI 0.03 to 0.92)** Communication 10.2% CBZ vs LMT OR 2.91 (95% CI 0.64 to 13.21) CBZ vs VPA OR 0.68 (95% CI 0.15 to 3.05) Daily Living Skills 5.1% CBZ vs LMT OR 0.64 (95% CI 0.15 to 2.75) CBZ vs VPA OR 0.48 (95% CI 0.09 to 2.66) **Socialization** 5.1% CBZ vs LMT OR 1.54 (95% CI 0.18 to 13.15) **CBZ vs VPA** **OR 0.15** **(95% CI 0.02 to 1.00)** **Motor Skills** 8.2% CBZ vs LMT OR 0.81 (95% CI 0.19 to 3.41) **CBZ vs VPA** **OR 0.20** **(95% CI 0.05 to 0.82)** N=97	-	**ABC** **2.9%** **LMT vs VPA** **OR 0.11** **(95% CI 0.02-0.74)** Communication 7.7% LMT vs VPA OR 0.23 (95% CI 0.04-1.27) **Socialization** **4.8%** **LMT vs VPA** **OR 0.10** **(95% CI 0.01-0.89)** **Motor Skills** **7.7%** **LTG vs VPA** **OR 0.09** **(95% CI 0.02-0.50)** N=104	-	-				
Birth Registers									
Husebye et al. 2020 Prospective cohort study using data from the Norwegian Mother and Child Cohort Study Language impairment at 5 years Language impairment at 8 years AED-exposed children of WWE vs Children of women without epilepsy	Language impairment at 5 years aOR 1.9 (95% CI 0.6-5.6) **Language impairment at 8 years** **aOR 3.8 (95% CI 1.6-9.0)** N=23	-	Language impairment at 5 years aOR 1.0 (95% CI 0.5-2.3) Language impairment at 8 years aOR 1.2 (95% CI 0.6-2.6) N=41	Language impairment at 5 years aOR 1.0 (95% CI 0.2-5.3) Language impairment at 8 years aOR 0.7 (95% CI 0.1-6.0) N=6	-	-	-	Language impairment at 5 years aOR 5.8 (95% CI 0.5-64.0) Language impairment at 8 years aOR 1.1 (95% CI 0.1-10.9) N=4	Language impairment at 5 years aOR 2.2 (95% CI 0.7-7.0) Language impairment at 8 years aOR 2.2 (95% CI 0.7-6.4) N=16
Bech et al, 2018 Learning disabilities in 1st year of compulsory education Vs unexposed controls Or Vs AED exposed	cf Unexposed controls aOR 1.74 (95% CI 0.19 to 16.05) cf AED exposed aOR 0.46 (95% CI 0.06 to 3.79) N=35	cf Unexposed controls aOR 1.22 (95% CI 0.14 to 10.52) cf AED exposed aOR 0.31 (95% CI 0.04 to 2.58) N=29	cf Unexposed aOR 1.81 (95% CI 0.74 to 4.41) cf AED exposed aOR 0.42 (95% CI 0.19 to 0.92) LMT mono 290 exposures	**cf Unexposed aOR 13.17 (95% CI 1.581 to 109.99)** cf AED exposed aOR 5.45 (95% CI 0.78 to 38.02) N=12	cf Unexposed aOR 2.34 (95% CI 0.50 to 10.82) cf AED exposed aOR 0.88 (95% CI 0.24 to 3.27) N=44	**cf Unexposed aOR 57.36 (95% CI 4.63 to 710.21)** **cf AED exposed aOR 12.61 (95% CI 1.98 to 80.15)** N=11		**cf Unexposed aOR 5.82 (95% CI 1.21 to 27.97)** cf AED exposed aOR 2.57 (95% CI 0.67 to 9.89) N=27	**cf Unexposed aOR 5.31 (95% CI 2.03 to 13.93)** **cf AED exposed aOR 4.67 (95% CI 1.73 to 12.59)** **N=55**
Forsberg et al, 2011 Children's School Grade OR Not Passing Exams AED exposed versus	Maths OR 1.60 (95% CI 0.99-2.56) English OR 1.31 (95% CI 0.78-2.18) Swedish OR 1.32 (95% CI 0.81-2.17) Sport						Maths OR1.13 (95%CI 0.81-1.54) English OR1.16 (95%CI 0.81-1.66) Swedish OR1.17 (0.81-1.69) Sport OR 1.00 (95%CI 0.68-1.47)		

Other children born in the same period	OR 1.50 (95% CI 0.93-2.44) N=243						N=316		
Others									
Elkjaer et al, 2018 Performance in national tests Difference in standardised z scores AED vs No AED exposure	Danish 2nd grade -0.01 (-0.05 to 0.03) 4th grade -0.02 (-0.05 to 0.01) 6th grade -0.02 (-0.05 to 0.01) 8th grade -0.03 (-0.07 to 0.01) Mathematics 3rd grade -0.04 (-0.08 to 0.01) **6th grade -0.04 (-0.07 to -0.01)** N=294	-	- Danish 2nd grade -0.01 (-0.02 to 0.01) 4th grade 0.00 (-0.02 to 0.02) 6th grade 0.01 (-0.02 to 0.04) 8th grade 0.02 (-0.03 to 0.07 Mathematics 3rd grade 0.00 (-0.02 to 0.02) 6th grade 0.01 (-0.01 to 0.04) N=396		Danish 2nd grade -0.01 (-0.04 to 0.02) 4th grade -0.01 (-0.04 to 0.02) 6th grade -0.01 (-0.04 to 0.02) 8th grade -0.02 (-0.07 to 0.03) Mathematics 3rd grade -0.01 (-0.04 to 0.02) 6th grade -0.03 (-0.06 to 0.00) N=123				

7 Appendix 3

Table 3: Other Reproductive Toxic Effects for prioritised AEDs

Table 3a: Fetal Loss

Fetal Loss											
	Carbamazepine	**Gabapentin**	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Pregabalin**	**Topiramate**	**Valproate**	**Zonisamide**
Meta-analyses											
Veroniki et al, 2017a	OR 1.25 (0.73,2.36) N=3911	-	OR 1.38 (0.70,2.88) N=2540	OR 2.47 (0.50,10.15) N=28	OR 1.66 (0.50,4.50) N=567	OR 0.90 (0.44,1.93) N=407	OR 1.50 (0.85,2.91) N=618	-	**OR 23.58 (1.18,549.60)** **N=2**	**OR 1.83 (1.04,3.45)** N=2612	-ǂ
Pregnancy Registries											
Vajda et al, 2018 Vs WWE unexposed	**4.7%** N=404	-	3.67% N=382	1.55% N=129	5.26% N=19	-	2.38% N=42	-	1.96% N=51	3.17% N=284	-
Kerala Pregnancy Registry											
Trivedi et al, 2018 vs WWE unexposed	**5.8%** **N=465**	-	**8.3%** **N=48**	6.4% N=63	**8.9%** **N=56**	3.6% N=138	7.8% N=129	-	**45.4%** **N=11**	**7.1%** **N=322**	-
Birth Registers											
Bech et al, 2014 Vs WWE unexposed	14.4% N=409	-	13.6% N=1128	-	15.0% N=413	-	-	-	-	**15.8%*** **N=474**	
ǂArtama et al, 2013 Finland Vs WWOE (no AED exposure)	**11.6 (all)** **9.2 (mono)** **24.0 (poly)** N=1292 (all) 1084 (mono)	-	No cases	No cases	11.5 (all) **13.2 (mono)** 6.1 (poly) N=695 (all) 532 (mono)	-	No cases	-	-	10.6 (all) 9.9 (mono) 1.3 (poly) N=944 (all) 706 (mono)	-
Fujii et al, 2013		9.8% N=223 (71epilepsy)									
Others											
Winterfeld et al, 2016 Vs unexposed								15.1% N=139			
ǂOrnoy et al, 2008 Vs non-teratogen exposed women	-	-	-	-	-	-	-	-	**11.3%** N=52		

* Increased risk driven by high dose VPA (>750mg/.day)

Table 3b Preterm Birth

Preterm Birth											
	Carbamazepine	**Gabapentin**	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Pregabalin**	**Topiramate**	**Valproate**	**Zonisamide**
Meta-analyses											
Veroniki et al, 2017a	OR 1.10 (0.77,1.56) N=2141	OR 1.93 (0.88,4.05) N=76	OR 1.05 (0.70,1.48) N=3015	OR 0.87 (0.04,8.14) N=93	OR 0.80 (0.5,1.26) N=1045	OR 1.59 (0.87,2.75) N=206	OR 1.03 (0.55,1.82) N=283	-	OR 1.38 (0.73, 2.35) N=408	OR 0.96 (0.65,1.37) N=1694	-
Pregnancy Registries											
ǂHernandez-Diaz et al, 2014	**-**	-	5.9% N=1581	-	-	-	-	-	10.4% N=347	-	10.2% N=98
Birth Registers											
Margulis et al, 2019 Swedish Mean pregnancy duration days compared with LMT	-1.3 (95 % CI -2.3 to -0.3) use any time N= 1975 **-1.6 (95% CI -2.7 to -0.5) 1st trimester** N=1686	**-**	ref	-0.5 (95 % CI -2.6 to 1.6) any time N=213 -0.7 (95% CI -2.9 to -1.5) 1st trimester N=184	-	-	-	-1.1 (95 % CI -3.0 to 0.8) any time N=522 -1.8 (95% CI -3.7 to 0.2) 1st trimester N=484	-	-0.0 (95 % CI -1.2 to -1.2) any time N=985 -0.1 (95% CI -1.3 to -1.2) 1st trimester N=845	-
Danielsson et al, 2019	**10.6%** **N=243**	**-**	5.7% N=437	7.2% N=118	-	-	-	-	-	4.5% N=130	-
Killic et al, 2014	**8.4% (all)** **8.1% (mono)** N=416	12.1% (all) 12.5% (mono) N=91	**9.3% (all)** **9.4% (mono)** **N=1157**	5.6% (all) 3.8% (mono) N=72	6.2% (all) 6.5% (mono) N=405	10.8% (all) 10.4% (mono) N=111	-	22.2% (all) 23.1% (mono) N=18	4.7% (all) 8.5% (mono) N=129	7.6% (all) 6.7% (mono) N=461	0
ǂArtama et al, 2013 Finland	**7.5% (all)** 7.7% (mono) N=1292 N=1084 mono	-	4.3% (all) 4.6% (mono) N=345 N=173 mono	**10.7% (all)** 15.4% (mono) N=56 N=13 mono	4.6% (all) 4.4% (mono) N=695 N=532 mono	-	7.5% (all) 7.7% (mono) N=53 N=26 mono	-	-	5.7% (all) 5.7% (mono) N=944 N=706 mono	-
Fujii et al, 2013		10.5% N=223									
Others											
Mostacci et al, 2017	-	**54.5%** **N=11**	-	-	-	-	-	25% N=16	-	-	-
Winterfeld et al, 2016								9.2% N=119			
Ornoy et al, 2008	-								9.8% N=29		

Table 3c: Prenatal Growth Restriction

Prenatal Growth Restriction											
	Carbamazepine	**Gabapentin**	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbital**	**Phenytoin**	**Pregabalin**	**Topiramate**	**Valproate**	**Zonisamide**
Meta-analyses											
Veroniki et al, 2017a	OR 1.15 (0.77,1.67) N=2897	OR 1.37 (0.44,3.61) N=70	OR 0.90 (0.56,1.42) N=2882	OR 1.27 (3.04,3.54) N=81	OR 0.99 (0.56, 1.76) N=1002	**OR 1.88 (1.07,3.32)** N=400	OR 0.68 (0.37,1.21) N=519	-	**OR 2.64 (1.41, 4.63)** **N=472**	1.28 (0.86,1.95) N=1622	-
Pregnancy Registries											
North American Hernandez Diaz et al, 2017 Compared with LMT		aRR 1.2 (95% CI 0.7 to 2.0) N=153				**aRR 2.4 (95% CI 1.6 to 3.6)** N=178	aRR 0.8 (95% CI 0.5 to 1.25) N=383		**aRR 2.4 (95% CI 1.8 to 3.1)** N=394		**aRR 1.9 (95% CI 1.2 to 3.0)** N=125
ǂHernandez-Diaz et al, 2014 TPM and ZNS compared with LMT and unexposed control group	**-**	-	6.8% SGA N=1581	-	-	-	-	-	**17.9% SGA** **Mean lower BW of 221g** **Mean lesser birth length of 1cm** N=347	-	**12.2% SGA** **Mean lower BW of 202g** **Mean lesser birth length of 1cm** N=98
Birth Registers											
Margulis et al, 2019 Swedish BW (grams) Microcephaly – Birth Head circumference (cm)	**BW** **-69 (95% CI -112 to -26)** **any time** **-87 (95 % CI -133 to -40) 1st trimester use** N=1988 (any time) N=1699 (1st trimester) **Microcephaly** **-0.3 (95% CI -0.5 to -0.2)** **any time** **-0.4 (95% CI -0.6 to -0.3) 1st trimester** N=1883 (any time) N= 1605 (1st trimester)	**-**	ref	BW -79 (95% CI -166 to 8) any time -95 (95 % CI -189 to 2) 1st trimester N=215 (any time) N=186 (1st trimester) Microcephaly -0.2 (95% CI -0.5 to 0.0) any time -0.3 (95% CI -0.6 to 0.0) 1st trimester N=206 (any time) N=178 (1st trimester)	-	-	-	BW -83 (95% CI -63 to 3) any time -127 (95 % CI -210 to 44) 1st trimester N=528 (any time) N=489 (1st trimester) Microcephaly -0.0 (95% CI -0.3 to 0.2) any time -0.2 (95% CI -0.4 to -0.1) 1st trimester N=516 (any time) N=480 (1st trimester)	-	BW -27 (95% CI -79 to 24) any time -40 (95 % CI -95 to 14) 1st trimester N=992 any time N=852 1st trimester Microcephaly -0.2 (95% CI -0.3 to 0.0) any time -0.2 (95% CI -0.4 to 0.2) 1st trimester N=931 (any time) N=802 (1st trimester)	
Danielsson et al, 2019 SGA	2.9% N=243	**-**	1.8% N=437	3.4% N=118	-	-	-	-	-	2.3% N=130	-
ǂVeiby et al, 2014 SGA BW SGA HC	**SGA BW** **11.9%** **Vs** **9.6%** **aOR 1.37 (95% 1.09 to 1.73)** **SGA HC** **4.6%** **Vs** **2.4%**	-	SGA BW OR1.0 NS (CI not provided) SGA HC OR 1.1 NS (CI not provided) N=983	SGA BW OR0.8 NS (CI not provided) SGA HC OR 0.4 NS (CI not provided) N=188	-	-	-	-	**SGA-BW** **25.0% vs 8.9%** **aOR 3.29 (95% 1.70 to 6.39)** **SGA-HC** **14.9% vs 2.4%** **aOR 7.21 (95% CI 3.23 to 16.1)** **N=90**	SGA BW OR 0.9 NS (CI not provided) SGA HC OR 0.8 NS (CI not provided) N=410	

	aOR 2.05 (95% 1.44 to 2.93) N=704										
Killic et al, 2014 SGA LBW	**SGA** **13.5% (all)** 11.2% (mono) **LBW** **6.5% (all)** **6.6% (mono)** N=416	SGA 12.1% (all) 12.5% (mono) LBW 5.5% (all) 6.9% (mono) N=91	SGA 10.3% (all) 8.9% (mono) LBW **5.8% (all)** 5.5% (mono) N=1157	SGA 15.3% (all) 11.5% (mono) LBW 5.6% (all) 7.7% (mono) N=72	SGA 18.7% (all) 16.0% (mono) LBW **6.2% (all)** 5.5% (mono) N=405	SGA 18.9% (all) 18.8% (mono) LBW 9.9% (all) 9.4% (mono) N=111	SGA 38.5% (all) 20.0% (mono) LBW 7.7% (all) 20.0% (mono) N=13	SGA 27.8% (all) 23.1% (mono) LBW 16.7% (all) 15.4% (mono) N=18	**SGA** **23.3% (all)** 17.0% (mono) LBW 5.4% (all) 6.8% (mono) **N=129**	**SGA** **16.8% (all)** **15.3% (mono)** LBW **8.1% (all)** **6.5% (mono)** **N=461**	
ǂArtama et al, 2013 LBW SGA	**LBW** **5.2% (all)** **4.7% (mono)** SGA 2.3% (all) 1.8% (mono) N=1292 (all) 1084 (mono)	-	LBW 4.1% (all) 3.5% (mono) SGA 1.7% (all) 1.2% (mono) N=345 (all) 173 (mono)	**LBW** **10.7% (all)** **15.4% (mono)** SGA 3.6% (all) 0 (mono) N=56 (all) 13 (mono)	LBW 4.4% (all) 3.6% (mono) **SGA** 3.9% (all) **3.4% (mono)** N=695 (all) 532 (mono)	-	LBW 3.8% (all) 3.8% (mono) SGA 0 (all) 0 (mono) N=53 (all) 26 (mono)	-	-	LBW 4.6% (all) 4.0% (mono) SGA 1.9% (all) 1.7% (mono) N=944 (all) 706 (mono)	-
Fujii et al, 2013 IUGR LBW		**IUGR** **3.5%** **Vs** **1.9% control** **LBW 10.5%** **Vs** **4.4% control**									
Almgren et al, 2009 BW adjusted HC	**-0.15 mean SD +/- 0.03** **N=1094**	-0.02 +/- 0.13 N=56	-0.004 +/-0.06 N=308	-	-	-	-0.02 +/- 0.09 N=137	-	-	**-0.10 mean SDs +/- 0.05** N=460	-
Others											
Mostacci et al, 2017 SGA	-	**27%** **N=11**	-	-	-	-	6.3% N=30	-	-		
Winterfeld et al, 2016 Birth Weight g (median, IQR)								3,300 g (3,000 to 3,690) N=119			
ǂOrnoy et al, 2008 Birth weight (grams)	-	-	-	-	-	-	-	-	**2932g** **vs** **3300** N=52		

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Johnson & Johnson Study - SRT IIIC 3/8: Mouse teratology study (conducted in 1986)

Johnson & Johnson Study - SRT IIIC 5/8: Rat embryo-fetal study (conducted in 1986)

Johnson & Johnson Study - SRT IIIC 4/8: Rat embryo-fetal study (conducted in 1994)

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9 Glossary of Terms

Absence seizures
An absence seizure, which used to be called a "petit mal" seizure, is where the person loses awareness of their surroundings for a short time. They mainly affect children, but can happen at any age. During an absence seizure, a person may stare blankly into space.

Adjunctive treatment/therapy
Another treatment used together with the primary treatment. Its purpose is to assist the primary treatment.

Amygdala
Amygdala, region of the brain primarily associated with emotions, emotional behaviour, and motivation. It is sometimes referred to as the fear centre in the brain.

Antiepileptic drug or AED
A drug used to treat epilepsy, mainly by controlling or managing the occurrence of seizures in a patient with epilepsy.

Atrial septal defect
A birth defect affecting the heart where a baby is born is a hole in the wall (septum) that divides the two upper chambers (atria) of the heart.

Attention deficit hyperactivity disorder
ADHD is a mental health condition that is defined through analysis of behaviour. People with ADHD show a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with day-to-day functioning and/or development.

Autism spectrum disorder
Autism is a lifelong developmental disability which affects how people communicate and interact with the world. Autism is a spectrum condition and affects people in different ways.

Bipolar disorder
Bipolar disorder is a mental health condition that affects moods and can make them swing from one extreme to another. It used to be known as manic depression. People with bipolar disorder have episodes of depression (feeling very low and lethargic) and mania (feeling very high and overactive). Unlike simple mood swings, each extreme episode of bipolar disorder can last for several weeks (or even longer).

Cardiovascular
Relating to the heart and blood vessels.

Cleft lip or palate
A cleft is a gap or split in the upper lip or roof of the mouth (palate). Cleft lip and palate can each occur alone or together. It is the most common facial birth defect in the UK affecting around 1 in every 700 babies.

Clinical data or clinical studies
Data on the effects of medicines that come from studies of people taking the medicines. This includes data from **clinical trials** and **epidemiological studies**.

Clinical trial
A research study that tests the effectiveness and safety of medicines in humans.

Club foot
Club foot is a deformity of the foot and ankle that babies can be born with. A baby born with club foot has one or both feet pointing down and inwards with the sole of the foot facing backwards. The position and function of the foot can be greatly improved, if treated early. Club foot is quite common, affecting about 1 baby in every 1,000 born in the UK. Both feet are affected in about half of these babies.

Coarctation of the aorta
A birth defect in which a part of the aorta (the large blood vessel that carries blood from the heart to the rest of the body) is narrower than usual. This narrowing prevents the blood from circulating normally in the lower half of the body. If the narrowing is severe enough and if it is not diagnosed, the baby may have serious problems and may need surgery or other procedures soon after birth.

Cognitive abilities
Intellectual or thinking skills.

Cohort study
In a cohort study, a group of individuals exposed to a risk factor and a group who are unexposed to the risk factor are followed over time (often years) to determine the occurrence of disease. The incidence of disease in the exposed group is compared with the incidence of disease in the unexposed group.

Commission on Human Medicines
The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products..

Comorbidity/Comorbidities
Comorbidity means more than one disease or condition is present in the same person at the same time. Conditions described as comorbidities are often chronic or long-term conditions.

Confidence interval
A statistical range of numbers with a specific probability that a particular value lies within this range. Confidence intervals (CI) are used to assess the true difference in risk between two groups, and usually accompany ratio values such as **odds ratios**, hazard ratios and ‘observed versus expected’ ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant.

Confounds/confounding/confounded
Where people who receive a medicine are also more likely to have a particular risk factor then they may be more likely to develop a medical condition because of this risk factor and not because of the medicine. This can affect the results of epidemiological studies.

Congenital
A medical condition that is acquired by the **fetus** during pregnancy and is present at birth.

Congenital Malformations
A physical defect present in a baby at birth that can involve many different parts of the body, including the brain, heart, lungs, liver, bones, and intestinal tract.

Contra-indicated/Contraindication
When a drug should not be used in a specific situation, condition or group of people because it may be harmful to the person.

Control group
The control group is defined as the group in an experiment or study that does not receive the substance, drug, treatment that is being tested and is used by the researchers as a benchmark to measure how the other tested subjects do.

Cortex Cerebri
Also known as the cerebral cortex is the outer layer of neural tissue of the cerebrum (front brain) of the brain in humans and other mammals.

Craniofacial
Relating to the bones of the skull and face. Craniofacial abnormalities are birth defects of the face or head.

Craniosynostosis
A rare birth defect in where the baby’s skull doesn’t grow properly and their head becomes an unusual shape. It doesn’t always need to be treated but surgery can help if it is severe.

Cross sectional observational study
A study that involves looking at data from a population at one specific point in time. This type of study can be used to describe the characteristics that exist in a population and gather preliminary data to support further research but cannot be used to determine cause and effect.

Defect
A fault or imperfection in the body.

Developmental Delay
Where a child had not gained the developmental skills expected of them, compared to others of the same age. Delays may occur in the areas of motor function, speech language, cognition, play and social skills

Digit abnormalities
Birth defects of the fingers or toes.

Dyspraxia
Dyspraxia, also known as developmental co-ordination disorder (DCD), is a common disorder that affects movement and co-ordination. It does not affect intelligence but may make daily life more difficult. It can affect co-ordination skills –such as tasks requiring balance, playing sports or learning to drive a car – and fine motor skills, such as writing or using small objects.

Embryolethality
Death of an embryo, which can result in abortion/resorption of the embryo back into the mother's body.

Epidemiological studies
Studies which assess trends in the occurrence, distribution or control of diseases or medical conditions in defined populations.

Epilepsy
A brain condition characterised by fits or seizures.

Exposure misclassification
Misclassification (or classification error) happens when a participant is placed into the wrong population subgroup or category because of an observational or measurement error. When this happens, the true link between exposure and outcome is distorted. People may be placed in the wrong groups for different reasons including because of incomplete medical records, recording errors in medical records, or misinterpretation of records.

Fetal loss
For the purpose of clinical definition, pregnancy is divided into two halves, each of 20 weeks. Any pregnancy loss after 20 weeks, when the fetus is well-formed, is known as fetal loss.

Fetal head circumference
The size of the baby's head that can be measured during pregnancy and then compared to certain normal curves. Measurements can be taken with an ultrasound (also called a sonogram) that uses sound waves to show a picture of the baby and check on the baby's health and development.

Fetal hydantoin syndrome
A characteristic pattern of mental and physical birth defects that results from maternal use of the anti-epileptic drug phenytoin during pregnancy. The range and severity of associated abnormalities will vary greatly from one infant to another.

Fetus
An unborn baby developing in the mother's womb

Focal seizures
When an epileptic seizure starts in one side of the brain it's called a focal onset seizure or a focal seizure; both terns mean the same thing. Until recently these seizures were called partial seizures. When person has no loss of awareness of their surroundings during it, it is called a focal onset aware seizure. This type of seizure used to be called a simple partial seizure. When the person's awareness of what is happening around them is affected at any time during the seizure, it's called a focal impaired awareness seizure. This type of seizure used to be called a complex partial seizure.

Gastrointestinal system
This is the digestive system that includes

Generalised seizures
A generalised seizure starts when all areas of the brain are affected by an abnormal electrical impulse and happen without warning. There are different types of generalised seizures, including: absence seizures (petit mal seizures), myoclonic seizures, and clonic seizures. The person will be unconscious (except in myoclonic seizures), even if just for a few seconds and afterwards will not remember what happened during the seizure.

Gestational age
Gestational age is the common term used during pregnancy to describe how far along the pregnancy is. It is measured in weeks, from the first day of the woman's last menstrual cycle (period) to the current date. A normal pregnancy can range from 38 to 42 weeks.

Good Laboratory Practice
A set of rules and criteria intended to assure the quality and integrity of non-clinical laboratory studies.

Healthcare databases
Healthcare databases are systems into which healthcare providers routinely enter clinical and laboratory data during usual practice as a record of the patient's care.

Hippocampal neurons
Nerve cells found in a certain region of the brain (hippocampus) that is responsible for learning, emotions and memory.

Histopathological
Microscopic examination of tissues and/or cells in order to diagnose and study disease.

Human therapeutic dose - the dose of drug required to generate the desired therapeutic effect in humans

Hypospadias
A birth defect in boys where the opening of the urethra (the tube that carries urine from the bladder to the outside of the body) is not located at the tip of the penis.

Incidence
The occurrence of new cases of a disease or condition in a population over a specified time period.

Indication
The disease or condition, or manifestation or symptoms thereof, for which the drug is approved. As well as whether the drug is indicated for the treatment, prevention, mitigation, cure, relief, or diagnosis of that disease or condition.

Intelligence Quotient (IQ)
A total score derived from a set of standardized tests or subtests designed to assess human intelligence.

Intrauterine growth retardation/restriction
A condition where a baby is smaller than expected or when a baby's growth slows or stops during pregnancy

In-vitro study
An experiment or study, usually involving cells or tissues, which is conducted outside of a living organism in a controlled environment, such as a test tube or laboratory dish.

In-vivo study
A medical test, experiment or procedure that is done on (or in) a living organism, such as a laboratory animal or human.

In utero
The time that the fetus is in the uterus of the pregnant female.

Lennox-Gastaut syndrome
This syndrome usually begins between the ages of 3 and 5 but can start as late as adolescence. Children may have several different types of seizure with this syndrome. These include tonic (where the muscles suddenly become stiff), atonic (where the muscles suddenly relax), myoclonic, tonic clonic and atypical absences. Many children also develop learning difficulties as well as behaviour problems.

Major congenital malformations
Physical defects present in a baby at birth that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention.

Marketing authorisation holder
The company or other legal entity that has the authorisation to market a medicine in the UK.

Maternal toxicity
A toxic effect on a pregnant animal or woman or nursing mother, as opposed to one affecting an embryo, fetus, or nursing infant.

Median
The median is the “middle” value in a list of numbers placed in ascending or descending order.

Mental development index
Describes the mental development and behaviour of infants. Examples include the Bayley Scales of Infant Development that is used to describe the current developmental functioning of infants and to assist in diagnosis and treatment planning for infants with developmental delays or disabilities.

Meta-analysis
A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

Monotherapy
The treatment of a disease or condition with a single medicine.

Motor skills
Motor skills are movements and actions of the muscles to perform a specific task. Fine motor skills refer to small movements in the hands, wrists, fingers, feet, toes, lips and tongue. Gross motor skills involve motor development of muscles that enable babies to hold up their heads, sit and crawl, and eventually walk, run, jump and skip.

Microcephaly
A birth defect where a baby’s head is smaller than expected when compared with babies of the same sex and age.

Myoclonic seizures
Myoclonic means ‘muscle jerk’. Myoclonic seizures are brief but can happen in clusters (many happening close together in time), and often happen shortly after waking. They are classified as generalised seizures because the person is likely to have other seizures as well as myoclonic seizures.

National Birth Register
These are population-based registers that collect data from medical records about the prenatal, delivery and neonatal care of pregnant women and their offspring. Such registers support the monitoring of the health of pregnant women and their offspring and are used for research purposes.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Neonate
Newborn infant.

Neural
Relating to a nerve or the nervous system.

Neural tube defects
Neural tube defects are birth defects of the brain, spine, or spinal cord. The neural tube is the structure that eventually develops into the baby's brain and spinal cord. The neural tube starts to form in early pregnancy and closes about 4 weeks after conception. Spina bifida is a type of neural tube defect. In spina bifida, part of the neural tube does not develop or close properly, leading to defects in the spinal cord and bones of the spine (vertebrae).

Neurobehavioural effects
Conditions of or relating to the relationship between the action of the nervous system and behaviour. Examples of neurobehavioural effects include: poor memory, poor concentration, motor problems, etc

Neurodegenerative/Neurodegeneration
Gradual loss of structure or function of nerve cells in the brain (neurons), including death of the nerve cells. Neurodegenerative diseases can influence many functions including an individual’s movement, speech, memory, intelligence and more.

Neurodevelopment
A general term used to encompass the development of the nervous system.

Neurodevelopmental disorders and delay
A group of disorders in which the development of the central nervous system is disturbed. The disorders can affect emotion, learning ability, self-control and memory. They can also manifest as conditions such as attention deficit hyperactivity disorder or autism spectrum disorder.

Neurogenic
Effects or conditions giving rise to or arising from the nerves or the nervous system.

Neurons
Nerve cells that send information to each other by releasing chemicals, known as neurotransmitters, across junctions known as synapses.

Non-clinical studies
In drug development, preclinical development, also named preclinical studies and non-clinical studies, is a stage of research that begins before clinical trials (testing in humans) can begin, and during which important feasibility, iterative testing and drug safety data are collected. Used interchangeably with the term ‘pre-clinical studies’ within this report.

Odds ratio
A measure of risk for one group compared with another group. A value greater than 1 suggests an increased risk; a value equal to 1 suggests an equal risk; and a value less than one suggests a decreased risk.

Patient Information Leaflet
Every medicine pack includes a patient information leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties and the conditions attached to its use.

Partial seizures
See focal seizures.

Peripheral neuropathic pain
Neuropathic pain is the nerve pain that is experienced by those who have peripheral neuropathy. Peripheral neuropathy develops when nerves in the body's extremities, such as the hands, feet and arms, are damaged. The symptoms depend on which nerves are affected. The main symptoms of peripheral neuropathy include numbness and tingling in the feet or hands, burning stabbing or shooting pain in affected areas, loss of balance and co-ordination, and muscle weakness, especially in the feet.

Pervasive developmental disorders
A group of disorders characterized by delays in the development of socialization and communication skills. Parents may note symptoms as early as infancy, although the typical age of onset is before 3 years of age.

Polydactyly
Polydactyly is when a baby is born with one or more extra fingers or toes. It can be on one or both hands or feet. It is quite common, affecting about 1 baby in every 1,000 born in the UK.

Polytherapy
The treatment of a disease or a condition where two or more medicines are used at the same time. The term is most often used to describe treatment of epilepsy with more than one drug.

Postnatal
Relating to or denoting the period after childbirth.

Pregnancy Prevention Programme
A Pregnancy Prevention Programme is a set of measures that are intended to minimise the risk for the both the women and the unborn baby associated with the use of a medicine in women of childbearing age and during pregnancy.

Pregnancy Registry
A study that collects health information from women who take prescription medicines or vaccines when they are pregnant. Information is also collected on the newborn baby.

Prenatal
Before birth, during or relating to pregnancy.

Prescription cost analysis data
Prescription Cost Analysis (PCA) data shows national prescription data dispensed in the community in England. A prescription item refers to a single medicine prescribed by a doctor (or dentist/nurse/etc.) on a prescription form.

Preterm birth
Preterm birth, also known as premature birth, is the birth of a baby at fewer than 37 weeks' gestational age, as opposed to the usual about 40 weeks.

Prevalence
The proportion of individuals in a defined population that have a disease or other health outcomes of interest at either a specified point in time (known as point prevalence) or during a specified period of time (period prevalence).

Prospective cohort study
A prospective study asks a specific study question (usually about how a particular exposure affects an outcome), recruits appropriate participants, and looks at the exposures and outcomes of interest in these people over the following months or years.

p-value
A measure of the statistical probability of an event occurring by chance. A smaller p-value suggests the event is less likely to be due toy chance; a larger p-value suggests the event is more likely to have occurred by random chance.

Randomised controlled clinical trial
A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention.

Regression analysis
Regression is a statistical method that attempts to determine the strength and character of the relationship between one dependent variable and a series of other variables.

Regulatory compliant study
A study that is conducted in line with the rules and standards that are defined by a regulatory authority, such as the Medicines and Healthcare products Regulatory Agency.

Residual confounding
Residual confounding occurs when a risk factor has not been adequately adjusted for in the statistical analysis. The consequence is that the estimated association is not the same as the true effect.

Respiratory system
The respiratory (breathing) system includes the nose, throat (pharynx), larynx, the windpipe (trachea), the lungs and the diaphragm.

Retrospective study
A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). A retrospective study looks backwards and examines the medical and lifestyle histories of the people in each group to learn what factors may be associated with a disease or condition that is established at the start of the study.

Risk factor
A substance or activity that increases the likelihood of someone developing an illness or medical condition.

Risk Ratio/Relative Risk
A risk ratio (RR), also called relative risk, compares the risk of a health event (disease, injury, risk factor, or death) among one group with the risk among another group.

Safety signal
A safety signal is defined as the information suggesting a new potential association or new aspects of a known association between medicines and adverse event(s) that warrant further investigation.

Seizure
Uncontrolled electrical activity in the brain that produces fits or convulsions of the body.

Small for gestational age
Small for gestational age is a term used to describe babies that are smaller than usual for the number of weeks of pregnancy.

Spontaneous abortion
Is the loss of a pregnancy naturally before 20 weeks of gestation.

Standard deviation
A measure of the amount of variation of a set of values.[1] A low standard deviation indicates that the values tend to be close to the mean (the average) of the set, while a high standard deviation indicates that the values are spread out over a wider range.

Statistical analysis
Statistical analysis is the collection and interpretation of data in order to uncover patterns and trends.

Statistical significance
A statistical interpretation of data that indicates that a result is unlikely to have occurred by chance.

Structural analog
A compound that has a similar structure to another compound but differs from it in respect of a certain component. Despite being similar in chemical structure, structural analogs can have very different physical, chemical, biochemical, or pharmacological properties.

Summary of Product Characteristics (SPC)
Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Systematic review
A review of the published scientific literature that aims to find as much as possible of the research relevant to a particular research question and based on appraisal of the research summarises the main findings (qualitative or quantitative).

Teratogen/ teratogenic
A teratogen is an agent that can disrupt the anatomical development of the embryo resulting in a birth defect.

Tertiary care
Tertiary care, is a level of health care obtained from specialist hospitals after referral from primary care (usually GPs) and secondary care (hospital and community care).

Tonic clonic seizures
The type of epileptic seizure most people recognise. There are two phases to these seizures. In the first phase the ‘tonic’ phase the person will lose consciousness and won’t be aware of what is happening, their muscles will go stiff and so they may fall (if standing) and also bite their tongue. In the second phase the ‘clonic’ phase their limbs will jerk quickly and rhythmically and they may lose control of their bladder and/or bowels. They are likely to feel confused or sleepy afterwards, and take a while to recover fully.

Trimester
One of the three 3-month periods that a human 9-month pregnancy can be divided into.

Visual spatial skills
Visual spatial skills are the ability to process visual stimuli to comprehend spatial relationships between objects and to visualize different scenarios or images. Visual spatial skills help individuals find their orientation in space through taking in information from the world around them and organizing that visual information to create an understanding of meaningful patterns. It is one of a number of cognitive functions that also include perception, attention, memory, motor skills and language.