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Agence nationale de sécurité du médicament
et des produits de santé

SYNTHESIS

Antiepileptics during pregnancy:
Current state of knowledge on the risk
of malformations and of
neurodevelopmental disorders

APRIL 2019

SUMMARY

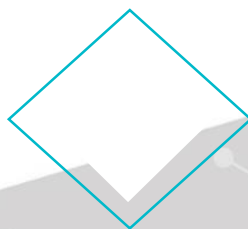Antiepileptics during pregnancy: Current state of knowledge on the risk of malformations and of neurodevelopmental disorders
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ABBREVIATIONS

MA	Marketing authorisation
CNAMTS	Caisse Nationale de l'Assurance Maladie des Travailleurs Salariés (French salaried workers health insurance fund)
CRAT	Centre de référence sur les agents tératogènes (Teratogenic agent reference centre)
CRPV	Centre régional de pharmacovigilance (Regional pharmacovigilance centre)
DCIR	Données Consommation Interrégimes (Inter-scheme consumption data)
MD	Mean difference
EURAP	European registry of antiepileptic drugs and International Registry of antiepileptic Drugs and Pregnancy
EUROCAT	European surveillance of congenital anomalies)
CI	Confidence interval
MACDP	Metropolitan Atlanta Congenital Defects Program
NAAED	North American antiepileptic drug Pregnancy Registry
OR	Odds ratio
DQ	Developmental Quotient
IQ	Intellectual Quotient
SPC	Summary of Product Characteristics
RR	Relative Risk
WA	Weeks' Amenorrhoea
SGA	Small for gestational age
Sniiram	Système national d'information inter-régimes de l'Assurance maladie (National health insurance inter-scheme information system)
ADHD	Attention deficit hyperactivity disorder
PDD	Pervasive Developmental Disorder
ASD	Autism spectrum disorder
UKEPR	United Kingdom and Ireland epilepsy and Pregnancy registers

BACKGROUND

In Europe, an estimated 2.6 to 6 million people have epilepsy. In terms of incidence, 2 to 5% of the general population is believed to be likely to experience an epileptic seizure, one third of which developing epilepsy, according to the old definition (at least two unprovoked (or reflex) seizures more than 24 hours apart). According to the studies, the standard incidence of epilepsy varies between 24 and 82/100,000 in Europe and between 44 and 162/100,000 in the United States. Distribution by age follows a bimodal law, with a higher incidence in children and the elderly. According to the studies, the prevalence of epilepsy varies between 3.3 and 7.8‰ inhabitants in Europe and between 2.7 and 6.8‰ inhabitants in the United States. As for the incidence, a higher prevalence is observed among children (0 – 5 years) and among the elderly (> 75 years) (Behr *et al.*, 2016). In France, 0.6 to 0.7% of the population is affected and in 75% of the cases, the

disease set in before the age of 18[1]. Thus in France an estimated 100,000 female patients are of childbearing age. It is estimated that, among the persons developing epilepsy around the world each year, 40% are between 15 and 60 years, and 0.3 to 0.7% of pregnancies occur in patients with balanced epilepsy (Rheims, 2011), most of them being treated with antiepileptics. Some of these drugs are also used in psychiatric illnesses (bipolar disorders) and neurological diseases (pain, migraine, etc.), which also affect young women (Elefant *et al.*, 2007). Faced with the public health challenges represented by the potential risks related to prenatal exposure to antiepileptics, the entire therapeutic group was analysed, in order to provide, at a given time, an overview of the data available on the risks of malformation and of neurodevelopmental disorders from these substances.

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OVERVIEW

Antiepileptic drugs during pregnancy: Current state of knowledge on the risk of malformation and neurodevelopmental disorders

◆ **Risks associated with antiepileptic drug exposure during pregnancy has to be considered before initiation of treatment;**

◆ Specialized medical advice should be given at female children, adolescents, and women of childbearing potential, and the antiepileptic treatment should be re-assessed regularly by a specialist.

◆ Before treatment initiation, women should be informed of the need to plan a pregnancy. The need of antiepileptic treatment should be re-assessed when a woman plans a pregnancy and be monitored carefully.

◆ Knowledge on the teratogenic and neurodevelopmental risk is highly variable depending on the antiepileptic and is constantly changing, which requires regular update and commands caution;

◆ Congenital malformations: if no risk can be fully ruled out, the risk level can be ordered according to antiepileptic (especially by comparison to the overall "standard" frequency observed in the general population[1]);

◆ Neurodevelopmental disorders: regardless of the antiepileptic, the data is highly limited and does not make it possible to come to a final conclusion (outside the confirmed and high risk concerning valproate);

◆ **Valproate is the antiepileptic which causes the most malformations. It also leads to a high risk of neurodevelopmental disorders (cognitive and behavioural);**

◆ Other than valproate, two substances have, to date in France, a particularly preoccupying safety profile during pregnancy, due to their risk **and** use profile:

- **Topiramate** (EPITOMAX® and generics):
  - **Confirmed teratogenicity** with an overall frequency of malformations that is 3 times higher than in the general population (with, in particular, an increased risk of oral clefts and hypospadias) and **existence of a potential risk (signal) of neurodevelopmental disorders**
  - exposure mainly among women (around ¾ of patients age 15 to 49 years are women), high level of exposure (~ 30,000 women of childbearing age treated in 2017), increasing over time and off-label uses identified (especially for slimming and in bipolar disorder)
- **Pregabalin** (LYRICA® and generics) (and structurally-similar gabapentin):
  - Potential risk of malformations in the event of exposure during pregnancy
  - Very high level of exposure (~ 140,000 women of childbearing age treated in 2017), increasing over time, with multiple indications and off-label uses identified (especially in non-neuropathic pain).

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[1] In the general population and independently of drug exposure, the overall frequency of malformations is around 2-3%.

FIGURE 1 :
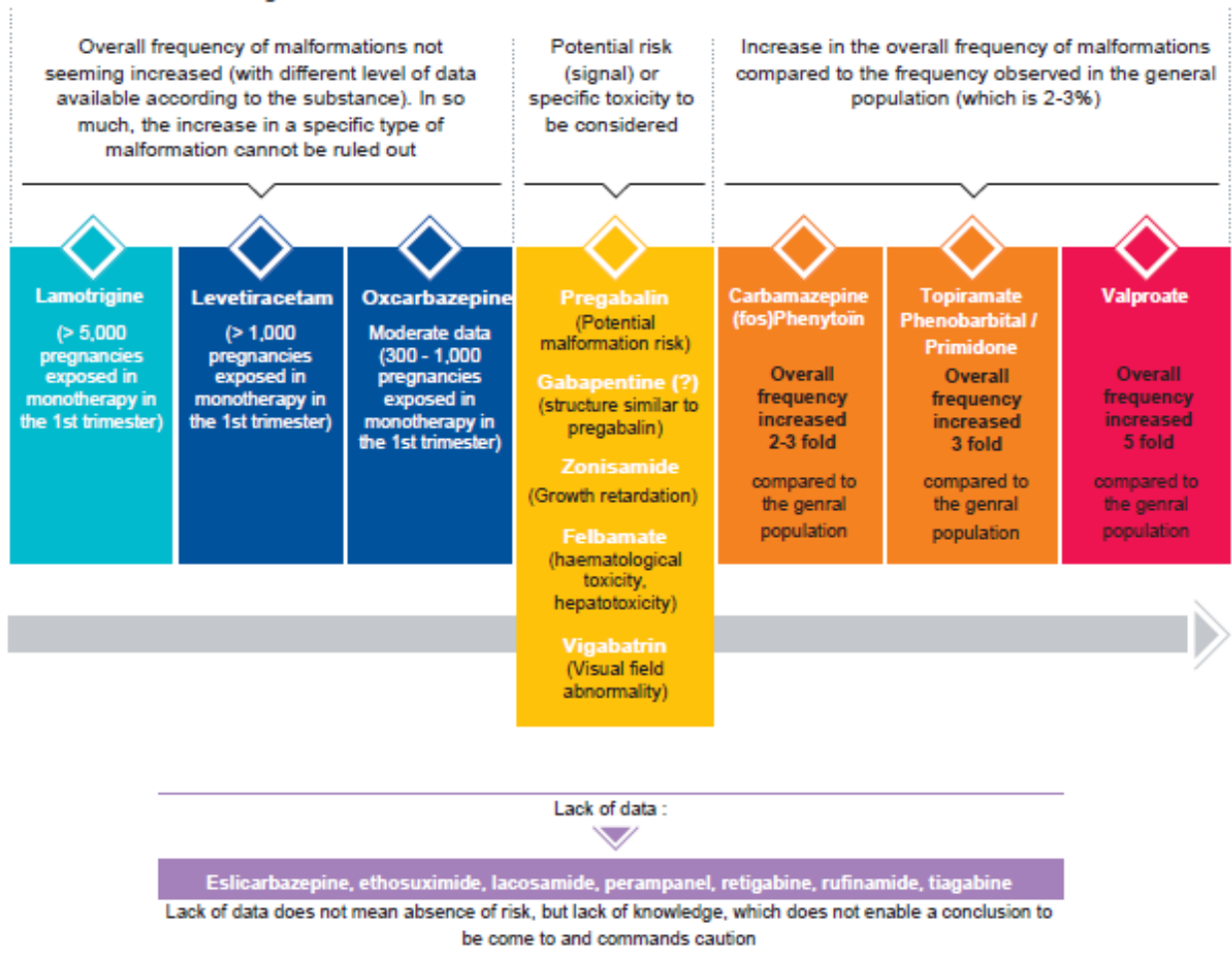Current state of knowledge on the overall risk of malformations : overview[2]

Overall frequency of malformations not seeming increased (with different level of data available according to the substance). In so much, the increase in a specific type of malformation cannot be ruled out			Potential risk (signal) or specific toxicity to be considered	Increase in the overall frequency of malformations compared to the frequency observed in the general population (which is 2-3%)		
Lamotrigine (> 5,000 pregnancies exposed in monotherapy in the 1st trimester)	**Levetiracetam** (> 1,000 pregnancies exposed in monotherapy in the 1st trimester)	**Oxcarbazepine** Moderate data (300 - 1,000 pregnancies exposed in monotherapy in the 1st trimester)	**Pregabalin** (Potential malformation risk) **Gabapentine (?)** (structure similar to pregabalin) **Zonisamide** (Growth retardation) **Felbamate** (haematological toxicity, hepatotoxicity) **Vigabatrin** (Visual field abnormality)	**Carbamazepine (fos)Phenytoin** Overall frequency increased 2-3 fold compared to the genral population	**Topiramate Phenobarbital / Primidone** Overall frequency increased 3 fold compared to the genral population	**Valproate** Overall frequency increased 5 fold compared to the genral population

Lack of data :

Eslicarbazepine, ethosuximide, lacosamide, perampanel, retigabine, rufinamide, tiagabine
Lack of data does not mean absence of risk, but lack of knowledge, which does not enable a conclusion to be come to and commands caution

FIGURE 2 :
Current state of knowledge on the overall risk of neurodevelopmental disorders : overview[2]

Too limited data to draw a definitive conclusion (no signal regarding IQ at the age of 6 years old)	Insufficient data to draw a conclusion	Risk not excluded, to be considered	Confirmed risk
Lamotrigine	Eslicarbazepine, ethosuximide, felbamate, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, pegabaline, retigabine, rufinamide, tiagabine, vigabatrin, zonisamide	Topiramate, Carbamazepine, Phenobarbital, Primidone, (fos)phenytoin	Valproate

(2) At the date of writing this report in april 2018.

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Pregnancy in a woman treated with an antiepileptic: management and follow-up

In the light of the risks identified and the data missing for a certain number of antiepileptics and/or types of disorders (especially neurodevelopmental), the most appropriate method of management of the patient's disease should be chosen and that which raises the lease concern for the unborn child.

Therefore it is essential:

◆ To rule out off-label use of antiepileptics where it does not meet the approved indications and conditions of the MA

◆ To discuss the possibility of pregnancy when treatment is started in a teenage girl or woman of childbearing age, then regularly in order to prevent unwanted pregnancy and to plan a pregnancy (information, contraception, planning)

◆ Where a woman treated wishes to become pregnant:

- Arrange a multidisciplinary pre-conception visit

- Reconsider, in all cases, the need for treatment (by a disease specialist), while envisaging discontinuation and if the mother's condition does not permit it, envisage any adjustments required (choice of treatment while taking the possible alternatives into consideration, reduction of the number of substances, of the dosage etc.)

◆ Monitor the pregnancy as far as possible, by multidisciplinary supervision, with communication of the patient's information and liaison between all the health care professionals monitoring the pregnancy, the newborn baby then the child, for implementation of reinforced and appropriate prenatal f, neonatal and post-natal follow-up

◆ Contribute to the monitoring systems (by reporting pregnancies, whether there are adverse effects or not, and this as soon as the pregnancy is diagnosed) in order to improve the risk assessment for these drugs during the pregnancy.

	KEY MESSAGES FOR MANAGEMENT
In all cases	◆ **The patient should not stop or change treatment without a doctor's advice as it can be dangerous for her and her unborn child if she is pregnant** ◆ **The MA indications and conditions should be followed** ◆ The patient should see a specialist as soon as possible if she is pregnant, believes she is pregnant or plans to become pregnant ◆ The risks should be taken into account in the choice of antiepileptic treatment, as soon as it is started
If pregnancy is not planned	◆ **Information from initiation of the treatment and throughout the patient's treatment on the potential risks and need for pregnancy to be planned** ◆ Regular reassessment by a specialist ◆ Effective and appropriate contraception during the treatment (bearing in mind that certain antiepileptics decrease the efficacy of hormonal contraceptives)
Where pregnancy is planned	◆ Pre-conception consultation, **multidisciplinary team** ◆ **Re-assessment of the usefulness of the treatment, discontinuation to be envisaged** ◆ If treatment necessary: information, modification, adjustment: • information for the patient and her partner • most appropriate treatment for management of the patient's disease and for which the clinical experience is the most extensive and raises the least concern for the unborn child • Minimum effective dose (based on, where possible, plasma concentrations, with baseline testing before pregnancy or very early on in pregnancy) ◆ Folic acid supplementation before conception and at the start of pregnancy: as the benefit of this measure is not established for malformations related to teratogenic antiepileptics, pre and postnatal follow-up shall be identical, whether the patient received it or not.
During the pregnancy	◆ **Reinforced follow-up by the disease specialist** (modification and/or adjustment of the treatment if necessary; vitamin D supplementation if necessary; etc.) ◆ **Obstetrical monitoring of high-risk pregnancies** (specialist and targeted prenatal surveillance)
Birth and immediately *post partum*	◆ Prevention of haemorrhagic syndrome: vitamin K ◆ Information for the maternity team for initiation of suitable monitoring of neonatal disorders ◆ Dose readjustment if changed during the pregnancy
Post natal	◆ Information for the health care professionals treating the child in order to initiate appropriate post natal monitoring and, if necessary, evaluate the child as soon as possible
Contribution to monitoring systems	◆ Reporting of adverse effects to the regional pharmacovigilance centres (CRPV) ◆ Registration of treated patients in specific registers or cohorts(i.e.: regional pharmacovigilance centres database (CRPV, TERAPPEL database), in the reference centre on teratogenic agents (CRAT), international antiepileptic and pregnancy registry (EURAP))
In the event of questions	◆ Do not hesitate to contact a regional pharmacovigilance centre (CRPV) or teratogenic agent reference centre (CRAT) for information

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MATERIAL AND METHODS

Data examined

Data available on 1st September 2015 relating to the risks of malformations and neurodevelopmental disorders in children exposed *in utero* to antiepileptic drugs was reviewed. The review is based on the data from scientific literature and on pharmacovigilance data from the marketing authorisation (MA) holders of the medicinal products in question. It should be noted that for the malformation risk, the substances for which a very large number of data is available in the registry studies (> 5,000 pregnancies exposed in the 1st trimester in monotherapy), only the most methodologically-robust data (studies with comparator groups, known exposure time, consideration of potential risk factors, study size etc.) was taken into account (the pharmacovigilance data was not). For substances of which the data available in literature are fewer than 300 pregnancies exposed in the 1st trimester, in monotherapy, data was extracted from the regional pharmacovigilance centre database (CRPV) on exposure during pregnancy (Terappel base).

It should be noted that, by default, unless otherwise specified in the text, the terms "malformation risk",

"malformations" or "congenital malformations" refer to major congenital malformations.

New studies published during assessment or writing of this report (between 1st September 2015 and June 2018) has been considered and taken into account if additional data were provided by these studies. As for instance, there are one meta-analysis on malformative risk published in 2016 (Weston *et al.*, 2016), a study related to neurodevelopmental disorders after *in utero* exposure to topiramate and levetiracetam (Bromley *et al.*, 2016), a study on the oral clefts after *in utero* exposure to topiramate (Hernandez-Diaz *et al.*, 2017), a study related to the risk of malformations after *in utero* exposure to pregabalin (Patorno *et al.*, 2017) et the update of the EURAP registry on many antiepileptic drugs (Tomson *et al.*, 2018). The results of pharmacoepidemiological studies conducted in 2017 and 2018 by ANSM/CNAM were also included in this report.

Antiepileptics examined

This report covers all drugs indicated in the treatment of epilepsy, except for valproate (the evaluation of which was conducted at European level), benzodiazepines (clobazam, clonazepam, diazepam and midazolam), corticosteroids and substances with indications only in infants (stiripentol). The following 21 substances were therefore examined: carbamazepine, eslicarbazepine, ethosuximide, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, tiagabine, topiramate, vigabatrin and zonisamide.

It should be noted that brivaracetam (Briviact®), marketing authorisation (MA) for which was granted in Europe in 2016, is not discussed in this report. The indications for these drugs differ (partial, generalised epilepsy, etc.) and some are also indicated in other illnesses, especially psychiatric (bipolar disorders) and/or neurological, other than epilepsy (pain, migraine, etc.).

Data on malformative and neurodevelopmental risks in children exposed to valproate in utero have not been reviewed in this report.

Working group

The evaluations conducted as part of this work were discussed in 3 working group "Pregnancy, reproduction and breastfeeding" sessions (on 08 April 2016; 7 July 2016 and 21 March 2017) during which the data available were presented and the conclusions submitted for discussion and approval.

Also, the members of the working group appointed as (co)rapporteurs re-read and approved the entire report.

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RESULTS

Exposure of women of childbearing age (15 - 49 years)

The data on exposure of women of childbearing age (15 - 49 years) to antiepileptics were extracted from the DCIR (inter-scheme consumption data) and from the Sniiram (Système national d'information inter-régimes de l'Assurance maladie- National health insurance inter-scheme information system). This database contains the individual data for reimbursement of treatment dispensed in private practices and private healthcare centres for beneficiaries of the main French health insurance schemes. The number of patients of childbearing age (15 - 49 years) with at least one prescription in 2017 is shown on the figure below. The change in the exposure data over time, over the period 2006 – 2017, is reported in appendix 1.

FIGURE 3 : NUMBER OF PATIENTS OF CHILBEARING AGE (15-49 YEARS) HAVING RECEIVED AT LEAST ONE PRESCRIPTION IN 2017
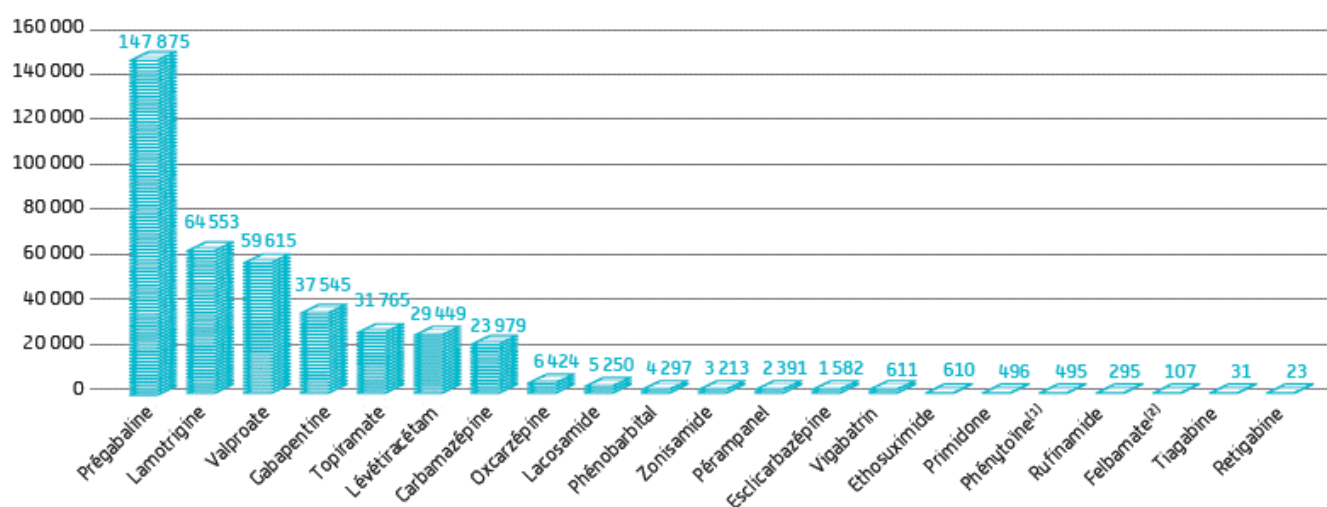
(1) Phenytoin: data not provided due to stock shortage since 20 March 2014. Fosphenytoin: data not accessible in the SNIIRAM (hospital reserve).
(2) Felbamate: only traced back to retrocession to hospitals.

Data relating to malformation and neurodevelopmental risks

The level of knowledge and the level of risk differ according to the antiepileptic and the type of disorders:

◆ **Malformation risk:** according to the antiepileptic examined, the data available ranges from almost non-existent (~10 pregnancies exposed in the 1st trimester with known outcome and prospective follow-up) to highly numerous (> 5,000 pregnancies exposed in the 1st trimester with known outcome and prospective follow-up). Nevertheless, among the antiepileptics for which data are available, the level of risk identified to date can be ordered (confirmed risk; potential risk (signal) or no signal identified to date).

◆ **Neurodevelopmental risk:** regardless of the antiepileptic examined, there is fewer data available than for the malformation risk. Therefore, in the current state of knowledge, and regardless of the antiepileptic examined, the data is too limited to enable a final conclusion to be made (outside the confirmed and high risk concerning valproate). Nevertheless, among the antiepileptics for which data are available (few data); the level of risk identified to date is different.

An overview of the data available and of the levels of risk identified to date is provided in the following tables. It should be noted that even if valproate is not discussed in this report, it is listed in the following tables for comparison purposes and on the databases from the European re-evaluation in 2014. A factual summary of the data available for each of the substances evaluated is reported in Appendix 2.

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TABLE 1: SUMMARY OF THE RATES OF MALFORMATIONS OBSERVED FOR ANTIEPILEPTICS IN THE REGISTERS AND META-ANALYSES

Only the data from the registry studies ("antiepileptics and pregnancy" or population) and from the meta-analyses, evaluating, in the same study, the impact of several antiepileptics are reported here. Therefore, the other types of studies or studies specifically covering an antiepileptic are not reported in this table.

	OVERALL FREQUENCY OF MALFORMATIONS: % (95% CI WHERE SPECIFIED) (n/N)						
	Valproate	Carbamazepine	Lamotrigine	Phenytoin	Phenobarbital	Levetiracetam	Oxcarbazepin
Antiepileptics and pregnancy registers							
EURAP (Tomson et al., 2018) - T1 International (42 countries)	10,3% (8,8 - 12,0) (142/1 381)	5,5% (4,5 - 6,6) (107/1 957)	2,9% (2,3 - 3,7) (74/2 517)	6,4% (2,8 - 12,2) (8/125)	6,5% (4,2 - 9,9) (19/294)	2,8% (1,7 - 4,5) (17/599)	3,0% (1,4 - 5,4) (10/333)
NAAED (Hernández-Díaz et al., 2012) T1 - North-American	9,3% (6,4 - 13,0) (30/323)	3,0% (2,1 - 4,2) (31/1 033)	2,0% (1,4 - 2,8) (31/1 562)	2,9% (1,5 - 5,0) (12/416)	5,5% (2,8 - 9,7) (11/199)	2,4% (1,2 - 4,3) (11/450)	2,2% (0,6 - 5,5) (4/182)
UKEPR (Campbell et al., 2014 ; Morrow et al., 2006) - T1 - Ireland and United Kingdom	6,7% (5,5 - 8,3) (82/1 220)	2,6% (1,9 - 3,5) (43/1 657)	2,3% (1,8 - 3,1) (49/2 098)	3,7% (1,3 - 10,2) (3/82)	/	/ (0,0 - 14,9) (0/22)	/
Registre Australien (Vajda et al., 2014 et 2016) T1	13,6% (37/272)	5,08% (20/394)	3,65% (13/356)	2,4% (1/41)	0% (0/4)[5]	1,89% (2/106)	5,9% (1/17)
Registry specific to an antiepileptic (pharmaceutical companies) T1	/	/	2,2% (1,6 - 3,1) (35/1 558)[3]	/	/	/	/
Population registers							
Norwegian births register (Veiby et al., 2014) During pregnancy	6,3% (21/333)	2,9% (20/685)	3,4% (np) (28/833)	0%[4] (0/37)[4]	7,4% (2/27)	1,7% (2/118)	1,8% (1/57)
Finnish register of birth (Artama et al., 2005) T1 - (Minor and major malformations))	10,6% (28/263)	2,7% (22/805)	/	2,6% (1/38)	/	/	1,0% (1/99)
Swedish births register (Källén et al., 2013) Start of pregnancy	8,9% (62/697)	3,8% (58/1 511)	3,4% (ns) (37/1 084)	8,6% (12/140)	11,8% (2/17)	1,8% (1/57)	10,0% (10/40)
Danish births register (Molgaard-Nielsen et al., 2011) T1 - (includes polytherapies)[4]	/	/	3,7%[4] (ns) (38/1 019)[4]	/	/	0%[4] (0/58)[4]	2,8%[4] (11/393)[4]
Icelandic births medical register (Olafsson et al., 1998) ns - (includes polytherapies)[4]	4,5%[4] (2/44)[4]	1,2%[4] (1/84)[4]	/	7,7%[4] (7/91)[4]	8,7%[4] (8/92)[4]	/	/
French data from national health insurance (ANSM/CNAM 2017) (26 major malformations) - T1	Epilepsy : 4,44% (41/924), BPD : 2,23% (16/719)	1,23% 6/467	1,36% 40/2 950	/	2,5% (2/80)	1,01% (6/594)	0,71% (1/140)
Meta-analysis							
Samren et al., 1997 Meta-analysis 5 studies[6] (Prospective)	9% (16/184)	8% (22/280)	/	6% (9/141)	10% (5/48)	/	/
Meador et al., 2008 (Minor and major malformations)	10,73% (8,16 - 13,29) (ns/2 097)	4,62% (3,48 - 5,76) (ns/4 411)	/	7,36% (3,60 - 11,11) (ns/1 198)	4,91% (3,22 - 6,59) (ns/945)	/	/
Weston et al., 2016 (until september 2015) (31 studies[7])	10,93% (8,9 - 13,13) (ns/2 565)	4,93% (3,84 - 6,16) (ns/4 666)	2,31% (1,87 - 2,78) (ns/4 195)	6,26% (4,37 - 8,47) (ns/1 279)	7,10% (5,36 - 9,08) (ns/709)	1,77% (0,98 - 2,79) (ns/817)	2,39% (0,85 - 4,68) (ns/238)

(1) Phenobarbitone et primidone
(2) Cunnington et al., 2011
(3) Montouris et al., 2003
(4) Mono- et polytherapy
(5) not mentioned by the authors, found from the data provided in the publicatio
(6) Studies included : Koch et al., 1992 ; Kappe. et al., 1986 and 1988, Heisaaa et al., 1982 ; Omtzor et al., 1992 et Lindhout et al., 1984 (7)
31 studies: prospective cohorts, cohorts based on "pregnancy" registers and randomised clinical trials

Topiramate	Gabapentine	Pregabalin	Ethosuximde	Vigabatrin	Felbamate	Zonisamide	Controls	
							Non epileptic	Untreated epileptic
3,9% (1,5-8,4) (6/152)	2,8% (0,5-14,2) (1/36)	/ (0/4)	/ (0/12)	/ (0/4)	/ (0/3)	/ (0/9)	/	/
4,2% (2,4-6,8) (15/359)	0,7% (0,02-3,8) (1/148)	/	/		/	/ (0,0-3,3) (0/90)	1,1% (5/442)	/
7,1% (2,0-22,6) (2/28)	3,2% (0,6-16,2) (1/31)	/	/ (0/12)	/ (0/6)	/	/	/	2,4% (1,4-4,1) (13/541)
1,96% (1/51)	/ (0/14)	/	/ (0/4)	/ (0/1)	/	/	/	2,19% (4/183)
/	/ (0/11)[a]	/	/		/	/	/	/
4,2% (2/48)	/ (0/39)[a]	3,3% (1/30)	/	/ (0/14)[a]	/	/	2,9% (22 371/ 771 412)[b]	2,8% (106/ 3 773)[a]
/	/	/	/	/	/	/	/	2,8% (26/939)
12,2% (6/49)	1,7% (2/119)	/	8,3% (1/12)	/ (0/3)	/	33% (1/3)	3,1% (49 499/ 1 575 847)	/
4,6%[a] (5/108)[a]	1,7%[a] (1/59)[a]	/	/	/	/	/	2,4% (19 911/ 836 263)	/
/	/	/	/	/	/	/	2,2%	4,8% (2/42)
2,3% (12/521)	0,54% (2/372)	1,48% (25/1 691)	/	/	/	/	0,99% (18 620/ 1 883 556)	
/	/	/	8% (1/13)	/	/	/	8% (12/158) (2 studies)	/
/	/	/	/	/	/	/	3,27% (1,37-5,17) (4 487/ 108 084)	/
4,28% (2,65-6,29) (ns/473)	1,47% (0,26-3,64) (ns/145)	/	/	/	/	0,28% (0,25-2,39) (ns/90)		/

CI : confidence interval ; T1 : exposure at least in the 1st trimester of pregnancy ; NS : not specify ; BPD : bipolar disorders

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TABLE 2 : COMPARISON TABLE OF MALFORMATION AND NEURODEVELOPMENTAL RISKS FOLLOWING *IN UTERO* EXPOSURE TO ANTIEPILEPTICS

	Malformation risks			Decreased hormonal contraceptive efficacy	Neurodevelopmental risks		Other risk factors identified
	Teratogenicity in animals	↗ in the **overall** frequency of **major** malformations [1]	Type of malformations the most overrepresented	Dose-effect relationship		Data available (order of magnitude)	Results / Conclusions	
Valproate	Yes	**x 4-5**	Neural tube defects, oral clefts, hypospadias, cardiac defects, facial dysmorphia, craniostenosis, renal and uro-genital defects, limb defects, multiple malformation syndromes	Yes	No	Few data (~ 100 pregnancies)	**Confirmed risk:** ♦ **reduced DQ/ID** ♦ **developmental delay** ♦ **autism spectrum disorder** Data suggest an increase in attention deficit/ hyperactivity disorder	Severe exposure
Topiramate	Yes	**x 3**	Oral clefts, hypospadias (+ low birth weight, growth retardation and small-for-gestational age, microcephalia)	The data tend towards a dose-effect relationship but it remains to be confirmed	Yes	Very few data	Potential risk (signal): Neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	♦ Severe exposure and ↗ ♦ Over-representation of the women ♦ Off-label
Phenobarbital / Primidone	Yes	**x 3**	Cardiac, oral clefts, hypospadias, facial dysmorphia, hand and foot deformities (including hypoplasia of the fingers), microcephalia	Dose-effect relationship suggested but it remains to be confirmed	Yes	(Very) few data	Contradictory studies, neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	
Phenytoin / fosphenytoin	Yes	**x 2-3**	Cardiac, oral clefts, hypospadias, facial dysmorphia, hand and foot deformities (including hypoplasia of the fingers), microcephalia	Lack of data	Yes	Very) few data	Contradictory studies, neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	
Carbamazepine	Yes	**Up to x-3**	Neural tube defect, cardiac, oral clefts, hypospadias, facial dysmorphia, microcephalia, hand and foot deformities (including hypoplasia of the fingers)	The data tend towards a dose-effect relationship	Yes	Few data (~ 100 pregnancies)	Contradictory studies, neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	Severe exposure
Pregabalin	Yes	**Potential risk (signal)** - Few data (< 200 pregnancies[2]) (Central nervous system?)		Lack of data	No	Additional data requested	Data insufficient to be able to conclude	♦ Very severe exposure and ↗ ♦ Off-label
Gabapentine	Yes	Few data (~250 pregnancies[2]): insufficient to be able to conclude (Renal?)		Lack of data	No			♦ Very severe exposure and ↗ ♦ Off-label
Zonisamide	Yes	Data insufficient to conclude but specific risk profile to be considered: **growth retardation and small for gestational age**		Lack of data	No	Non-existent or almost non-existent	Non-existent or almost non-existent data: no conclusion possible	Off-label
Vigabatrin	Yes	Data insufficient to conclude but specific risk profile to be considered: **Visual field abnormality**		Lack of data	No study			
Felbamate	No	Data insufficient to conclude but specific risk profile to be considered: **Haematological toxicity / hepatoxoxicity**		Lack of data	Yes			

[1] *Increase* compared to the frequency observed in the general population (which is 2-3)

[2] *Number* of pregnancies exposed in the 1st trimester, collected prospectively.

	Malformation risks				Decreased hormonal contraceptive efficacy	Neurodevelopmental risks		Other risk factors identified
	Teratogenicity in animals	↗ in the **overall** frequency of **major** malformations [1]	Type of malformations the most overrepresented	Dose-effect relationship		Data available (order of magnitude)	Results / Conclusions	
Perampanel	To be reviewed	Data almost non-existent (< 10 pregnancies[2]) or very few (< 50 pregnancies[2]): no conclusion possible		Lack of data	Yes	Non-existent or almost non-existent	Non-existent or almost non-existent data: no conclusion possible	
Lacosamide	Insufficient				No			
Retigabine	Insufficient				No			
Eslicarbazepine	Yes				Yes			
Ethosuximide	Yes				No study			
Rufinamide	Yes				Yes			
Tiagabine	Yes				No			
Retigabine	To be reviewed				Yes			
Oxcarbazepine	Yes	The data available **(300 – 1,000 pregnancies [2])** do not agree with a substantial increase in the overall risk of major malformations. Further studies are required to confirm or disprove it.	Little or not studied	Lack of data	Yes	Data almost non-existent	Data insufficient to be able to conclude	Severe exposure
Levetiracetam	Yes	Data from main studies with appropriate methodology **(~ 1,000 pregnancies [2])** do not agree with a substantial increase in the overall risk of major malformations.	Little or not studied		No			
Lamotrigine	Yes	The data available **(> 5000 pregnancies [2])** do not agree with a substantial increase in the overall risk of major malformations.	Not applicable[3]	Dose-effect relationship reported in one study but not found in 3 other studies of the same size	Submission in DI WG meeting On 19 June 2017	Few data (~ 100)	Data too few to enable a final conclusion (no signal in terms of IQ, evaluated up to the age of 6)	Very severe exposure

[3] To date, over-representation of a specific type of malformations has not been demonstrated, nevertheless potential signals were identified occasionally in one study but not reported in the other studies; this means additional research is required (see section on lamotrigine)

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CONCLUSIONS

Malformation and neurodevelopmental risks

Pregnancy in a woman treated by antiepileptics can carry risks related to the antiepileptic treatment and/or related to the imbalance in the disease in the event of discontinuation or replacement of treatment. As it is a question of the risk of malformations or neurodevelopmental disorders related to the antiepileptic treatment, data currently available:

◆ Differs in terms of quality and methodologies. The most recent studies tend to be larger, report results for monotherapies and use more thorough methodological protocols with, in particular, blinded evaluations, more stringent inclusion criteria which decrease the selection bias, acknowledgement of relevant confounding factors, etc.

◆ Vary according to the antiepileptics examined and the types of disorders studied:

- For a certain number of substances, the data is missing or limited, not meaning there is no risk, but a lack of knowledge, and therefore no conclusion can be made. Caution needs to be exercised, as does regular data monitoring;
- Regardless of the antiepileptic examined, there are fewer data relating to neurodevelopmental disorders than for the malformation risk and they are too limited to enable a final conclusion (outside the confirmed and high risk concerning valproate).

◆ Show that the level of risk differs according to the antiepileptics. Therefore, among the antiepileptics for which there is the most clinical experience among pregnant women, the level of risk can be ordered according to the antiepileptics;

◆ Are constantly changing, meaning evaluations have to be regularly updated with regard to the progress in knowledge.

Neonatal risk

As stated in the "Materials and Methods" part, this risk was not re-evaluated for this work. Nevertheless, the possibility of occurrence of neonatal disorders is reiterated, depending on the antiepileptics examined, such as:

◆ Disorders related to impregnation and/or withdrawal, and effects related to the toxicity of the substance

◆ Haemorrhagic syndrome and the need for preventive vitamin K treatment

◆ Phosphocalcic/bone mineralisation impairment (possibly requiring vitamin D supplementation).

Risk of recurrence

The use of certain antiepileptics is associated with an increased risk of congenital malformations and/or neurodevelopmental disorders. Studies on antiepileptics "in general" (without differentiating the antiepileptic used) reported a risk of recurrence, namely that in a pregnant woman treated with an antiepileptic, the risk of having a child with a disorder is higher where an older sibling has it. This "overall" risk was around 39 to 55% according to these studies (Moore *et al*., 2000 and Dean

et al., 2002). More recent studies confirmed one (or more) siblings with malformations after exposure *in utero* to an antiepileptic to be a relapse risk factor (Campbell *et al*., 2013; Vajda *et al*., 2013; Veiby *et al*., 2014). The risk of malformations is all the higher the greater the number of siblings affected, and depends on the antiepileptic given during the pregnancy (higher risk identified especially for valproate, topiramate, phenobarbital and phenytoin).

Antiepileptic mono- *versus* polytherapy

Polytherapy with several antiepileptics can be related to a higher risk of congenital malformations than monotherapy. The risk related to polytherapy varies according to the concomitant antiepileptics administered and appears, in particular, higher with valproate (and topiramate) (Meador *et al*., 2008; Holmes

et al., 2011; Vajda *et al*., 2016). It should be noted that in view of the considerable number of antiepileptic combinations possible, evaluated of the risk for each of these combinations seems difficult, and in any case is not available within a short time frame (Pennell, 2016).

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Management

It is necessary to bear in mind that a woman of childbearing may be pregnant or likely to become pregnant. In effect, the period during which the risk of malformation is the highest often corresponds to a period during which the woman and the doctor are not yet aware of the pregnancy. Therefore, in women of childbearing age, these risks must be taken into account and explained as soon as antiepileptic treatment is started, regardless of the indication. In addition, close and specialist monitoring throughout treatment and early, appropriate and multidisciplinary management when pregnancy is desired are essential:

HEALTHCARE PATHWAY

Women of childbearing age treated with antiepileptics should receive a specialist medical opinion on a regular basis. To this effect:

◆ The treatment must be reassessed by a specialist of the disease:

- Regularly when pregnancy is not planned;
- Early on when a women is planning a pregnancy;
- As soon as possible in the event of pregnancy.

◆ Patients should be regularly informed from the start of treatment on the potential risks relating to drug exposure during the pregnancy and on the usefulness and need to plan a pregnancy;

◆ Effective and treatment-compatible contraception (taking drug interactions into account, may render the hormonal contraception ineffective), should be started.

PRE-CONCEPTION PHASE

Essential step aiming to take the necessary measures for reducing the harmful effects of drugs for the foetus while avoiding unbalancing the disease treated as far as possible. It involves planning the pregnancy far enough in advance to enable appropriate multidisciplinary management, including:

◆ A pre-conception visit during which information is shared between the various contributors managing the pregnancy together;

◆ Clear information for the patient and her partner;

◆ Folic acid supplementation before conception and at the start of the pregnancy. As the benefit of this measure is not established (the data available not demonstrating a preventive effect from folic acids on malformations related to teratogenic antiepileptics), pre and postnatal follow-up will be identical, whether the patient has received it or not.

◆ Careful reassessment of the antiepileptic treatment in place (by a specialist and multidisciplinary team if necessary) while maintaining disease balance. This step serves to assess the very usefulness of the treatment and to consider any possible alternatives. Where treatment is required during the pregnancy, it is necessary to:

- Inform: explain the choice of treatment to the patient and her partner: the expected benefits and the potential risks for the unborn child;
- Modify: choose the most appropriate treatment for management of the patient's disease and for which the clinical experience is the most extensive in pregnant women and raises the least concern for the unborn child;
- Adjust: use the minimum effective dose (based on, where possible, plasma concentrations, with baseline testing before pregnancy or very early on in pregnancy), for the shortest possible time;
- Monitor: set up close multidsciplinary monitoring in the prenatal, neonatal and/or postnatal period.

CLOSER PREGNANCY MONITORING

Multidisciplinary step with obstetrical monitoring of high-risk pregnancies and initiation of specialist-oriented monitoring, along with tighter neurological monitoring and adjustment of the antiepileptic treatment and supplementation if necessary. The question of breastfeeding should be discussed during the pregnancy.

IMMEDIATE POST-PARTUM MONITORING

◆ Management of the newborn should take account of the possible occurrence of neonatal disorders;

◆ Readjustment, if necessary, of the treatment modified during the pregnancy (especially the posology);

POST-NATAL FOLLOW-UP

This involves drawing the attention of health care professionals and patients to the potential risk of neurodevelopmental disorders in children exposed *in utero* in order for the child to be assessed as early as possible, in the event of doubt.

Do not hesitate to contact a regional pharmacovigilance centre (CRPV) or teratogenic agent reference centre (CRAT) for information, they will be able to provide you with expert, personalised opinions, on drug-related risks for a woman and her baby.

Risks related to sudden treatment discontinuation

Women of childbearing age treated with antiepileptics should not stop or change their treatment under any circumstances, without the advice of their prescriber. In particular, with epilepsy, antiepileptic treatment should not be discontinued suddenly as it can lead to onset of seizures, the consequences of which can be serious or even fatal for the mother and the foetus.

Non-compliant uses

Faced with these risks, and given the proof of use of certain antiepileptics in off-label therapeutic indications and the benefit/risk ratio of which is not as a result known, **health care professionals and patients are reminded of the need to rule out all use of antiepileptics in indications and/or conditions not approved by the MA.**

Need to monitor and collect data

In the light of the complexity of the subject, the lack of scientific data and importance of the subject in terms of public health, it would appear to be necessary to continue data collection, especially *via* the following three methods: reporting of cases to the pharmacovigilance system, recording of pregnancy patients in the relevant registry and conduct of *ad hoc* pharmaco-epidemiological studies.

REPORTING TO THE PHARMACOVIGILANCE SYSTEM

The clinical data on the risk relating to exposure during pregnancy are insufficient or even non-existent for most antiepileptics (especially for the most recent) or need to be completed for others. **Regardless of the antiepileptic in question, it is essential to** report:

◆ Cases of pregnant patients exposed to these drugs, from diagnosis of pregnancy, in order to ensure the prospective follow-up. Their registration in the specific regional pharmacovigilance centre databases (Terappel database) or databases of the reference centre on teratogenic agents (CRAT) contributes to enrichment of the data and to improving evaluation of the drug-related risk during pregnancy;

◆ The cases of adverse effects (in the case of pregnancy: any malformation, foetotoxic effect, neonatal effect or long-term effect) likely to be drug-related. The ANSM recalls that healthcare professionals should report them to their regional pharmacovigilance centre in their area. Patients and accredited patient associations can also report any adverse effects to their regional pharmacovigilance centre. For further information, see the "Reporting an adverse effect" section on the ANSM website: http://ansm.sante.fr (contact details of the regional pharmacovigilance centre) or via the link: Declaring adverse effects immediately.

"ANTIEPILEPTICS AND PREGNANCY" REGISTRY

Registration of pregnant patients by healthcare professionals. It should be noted that regular publication of the updated data of these registers appears necessary.

PHARMACO-EPIDEMIOLOGICAL STUDIES

A project for the pharmaco-epidemiological monitoring of exposure of women of childbearing age and pregnant women to treatments for bipolar disorder or epilepsy is planned.

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Change over time (2006 – 2017) in the annual number of patients of childbearing age (15 – 49 years) having had at least one prescription for an antiepileptic

Overt the period 2006 – 2017, the number of patients of childbearing age (15-49 years) with, in France, at least one prescription per year of prescription is described below :

NUMBER OF PATIENTS OF CHILDBEARING AGE (15-49 YEARS) WITH AT LEAST ONE PRESCRIPTION PER YEAR OF PRESCRIPTION
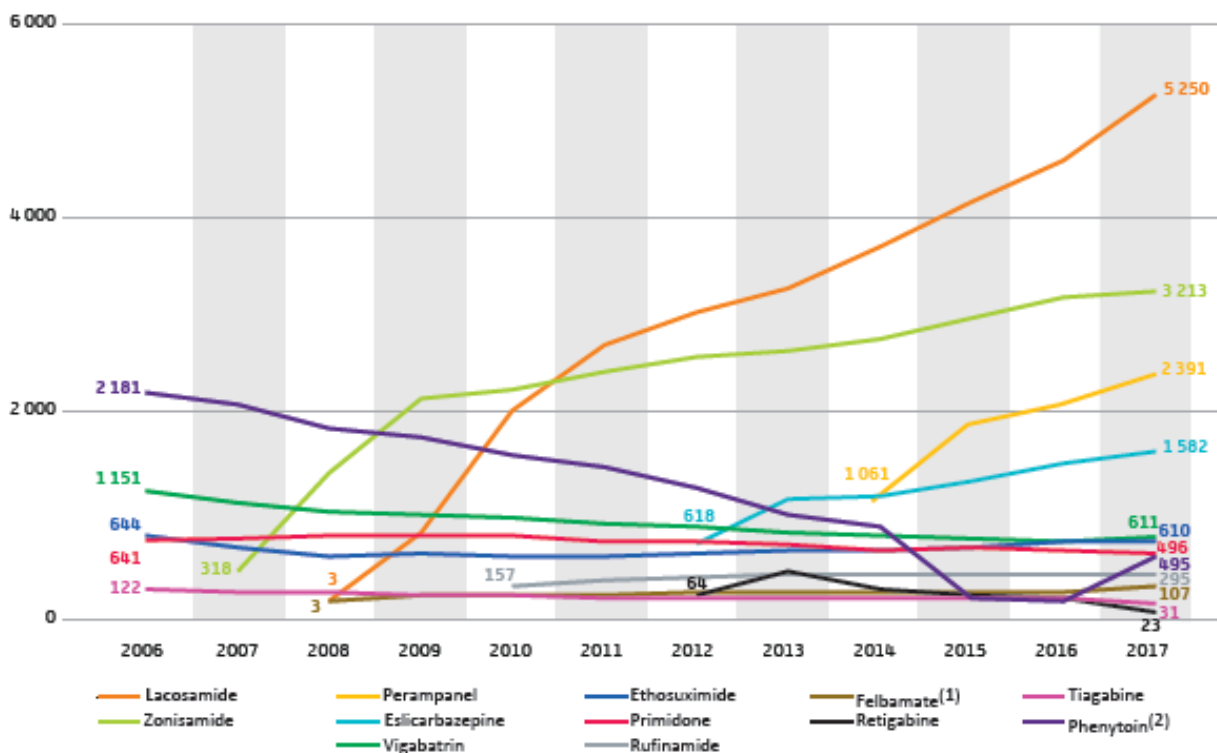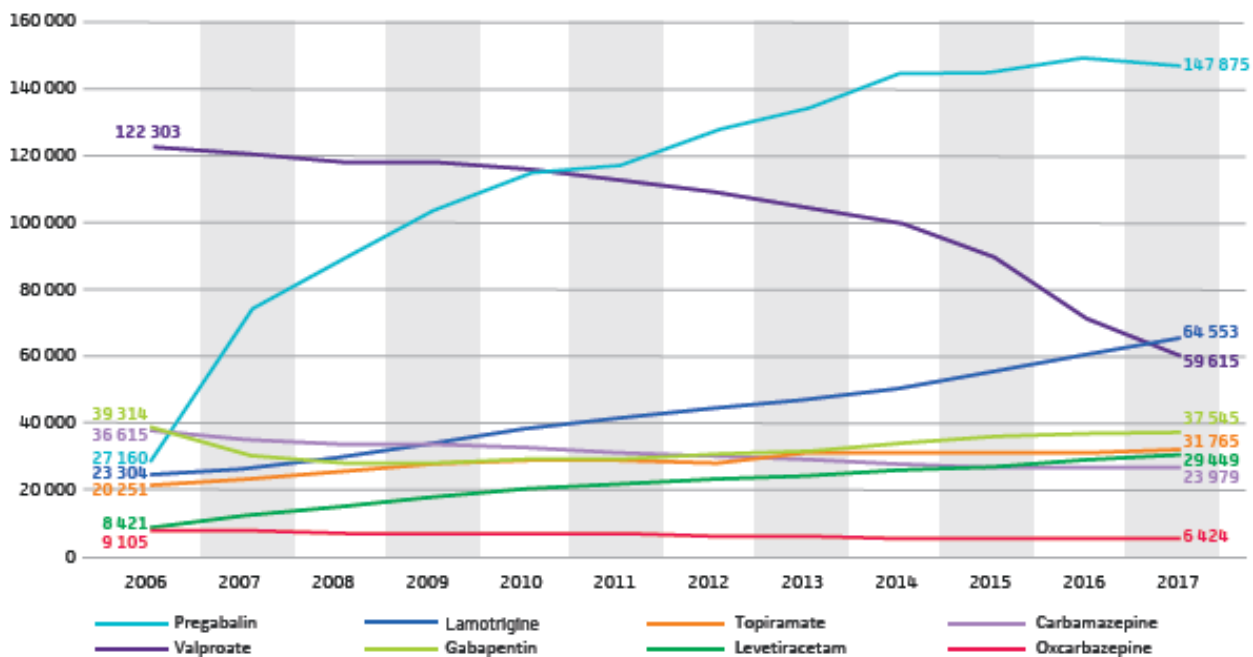
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Pregabalin	27 160	73 747	88 672	103 416	114 904	117 373	128 059	135 357	144 777	146 485	150 369	147 875
Valproate	122 303	119 848	117 326	117 546	115 562	112 017	108 264	103 434	99 306	89 170	69 959	59 615
Lamotrigine	23 304	25 533	28 276	33 292	37 001	40 610	43 715	46 346	49 855	54 145	59 696	64 553
Gabapentin	39 314	29 699	26 844	27 308	27 972	28 176	30 040	31 032	34 036	35 931	36 739	37 545
Topiramate	20 251	22 550	24 674	27 441	28 969	28 533	28 163	31 053	31 707	31 219	31 326	31 765
Levetiracetam	8 421	11 530	14 469	17 495	19 564	20 847	22 499	23 557	24 872	26 282	28 127	29 449
Carbamazepine	36 615	33 683	32 328	32 102	31 071	29 654	28 327	27 025	25 732	25 065	24 339	23 979
Oxcarbazepine	9 105	8 903	8 558	8 494	8 314	8 038	7 663	7 200	6 809	6 642	6 667	6 424
Phenobarbital	15 324	13 604	12 418	11 466	10 248	9 105	8 153	7 205	6 341	5 491	4 871	4 297
Lacosamide			3	720	1 987	2 672	3 014	3 244	3 690	4 128	4 577	5 250
Zonisamide		318	1 324	2 099	2 207	2 379	2 532	2 600	2 722	2 925	3 140	3 213
Perampanel									1 061	1 894	2 063	2 391
Eslicarbazepine							618	1 081	1 120	1 280	1 467	1 582
Vigabatrin	1 151	1 038	940	915	871	802	772	721	686	640	633	611
Ethosuximide	644	554	472	495	473	481	513	546	527	567	609	610
Primidone	641	641	671	694	684	629	617	584	545	556	520	496
Rufinamide					157	213	248	274	278	285	292	295
Felbamate[1]			3	74	82	84	90	89	85	98	96	107
Rétigabine							64	330	127	59	41	23
Tiagabine	122	106	88	70	56	51	49	34	34	30	30	31
Phenytoïne[2]	2 181	2 038	1 800	1 691	1 514	1 398	1 172	913	772	44	19	495

(1) Felbamate : Only retraced by hospital retrocession
(2) Phenytoin : Stock shortage since 20 March 2014.
Fosphenytoin : the data cannot be accessed in the Sniiram (hospital reserve).

NUMBER OF PATIENTS OF CHILDBEARING AGE (15-49 YEARS) WITH AT LEAST ONE PRESCRIPTION PER YEAR

(1) Felbamate : Only retraced by hospital retrocession
(2) Phenytoin : Stock shortage since 20 March 2014.
Fosphenytoin : the data cannot be accessed in the Sniiram (hospital reserve).

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APPENDIX 2

Factual summary of the data available for each antiepileptic evaluated

The data available on the malformation and neurodevelopmental risk was reviewed. Only the conclusions are reported below, therefore not all the literature references are provided here.

CARBAMAZEPIN

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Overall frequency of malformations

According to the data currently available from the registers, the overall frequency of occurrence of major malformations in children exposed *in utero* to carbamazepine monotherapy varies between 2.6% and 5.6% (Wide *et al*., 2004 and Kallen *et al*., 2013; Artama *et al*., 2005; Tomson *et al*., 2011; Hernandez-Diaz *et al*., 2012; Vajda *et al*., 2016; Veiby *et al*., 2014; Campbell *et al*., 2014). This variability may be related to the methodological differences between the studies, to the doses administered, etc. As the overall frequency of malformations in the general population is 2-3 %, exposure *in utero* to carbamazepine leads to, depending on the study, an overall frequency of malformations either similar to the general population, or 2 to 3 times higher than it. According to the meta-analyses conducted by Weston *et al*., 2016, children exposed *in utero* to carbamazepine have an average rate of malformation of 4.93% (3.84% – 6.16%; n = 4,666; 30 studies), therefore a risk 1.5 to 2 times higher than that of the non-exposed control groups (non-epileptic or epileptic).

By comparison with the lamotrigine-treated group, the data by Tomson *et al*., 2018 show a statistically significant higher risk in children exposed *in utero* to carbamazepine monotherapy (OR = 1.9 (1.4 - 2.6), calculated by the ANSM as not provided by the authors). This excess risk is not found in the Irish and British registers (Campbell *et al*., 2014), or in the North-American registry (Hernandez-Diaz *et al*., 2012). Among the 3 studies selected, having compared the overall frequency of malformations of children born to epileptic mothers treated with carbamazepine to that of non-epileptic patients, contradictory results come out, ranging from an absence of difference to a statistically-significant increase (RR = 2.7 (1.0 – 7.0); Hernandez-Diaz *et al*., 2012). The meta-analysis conducted by Weston *et al*., 2016 finds a statistically-significant increase in risk (RR = 2.01 (1.20 - 3.36); n = 1,367).

Conclusion on the overall frequency of malformations

Thus, in the current state of knowledge, follow-up of a very large number of pregnant women exposed to carbamazepine monotherapy in the 1st trimester of pregnancy (> 5,000 pregnancy outcomes) shows that carbamazepine can lead to an increase in the overall risk of major malformations, with an overall frequency of malformations either similar to, or up to 3 times that in the general population (which is 2-3%). If, after re-assessment, treatment is required, this risk is to be considered

in the choice of treatment and should be taken into account in the event of exposure during the pregnancy.

Types of malformations

♦ Data currently available show an increased risk of neural tube defects, especially spina bifida in children exposed *in utero* to carbamazepine, by comparison with children not exposed to antiepileptics (presenting or not presenting with other types of congenital malformations) (Rosa, 1991; Hernandez-Diaz *et al*., 2001 et 2007; Medveczky *et al*., 2004; Jentink *et al*., 2010; Werler *et al*., 2011; Gilboa *et al*., 2011). This increased risk is found in all case-control studies looking at this type of malformations and is multiplied by a factor of 2 to 14 according to the studies and the control groups. It should be noted that in the light of the low incidence of this type of malformations, case-control studies are the most capable of identifying an increased risk. Among the studies comparing or making a parallel with the frequency of occurrence of a neural tube defect, a lower frequency is observed after exposure *in utero* to carbamazepine, by comparison with valproate (Kallen *et al*., 1989; Arpino *et al*., 2000; Werler *et al*., 2011; Tomson et Battino, 2012). In contrast, an increased risk is reported among children exposed *in utero* to carbamazepine compared to the other antiepileptics examined (Rosa, 1991; Kallen *et al*., 1994; Lisi *et al*., 2010; Tomson et Battino, 2012) and in particular compared to lamotrigine (Tomson *et al*., 2011; Hernandez-Diaz *et al*., 2012 and Campbell *et al*., 2014).

♦ The data relating to the occurrence of cardiac malformations after exposure *in utero* to carbamazepine are contradictory. In effect, the case-control study looking at this type of malformation does not report a statistically-significant relationship between exposure *in utero* to carbamazepine monotherapy and the risk of cardiac malformations or coarctation of the aorta (Arpino *et al*., 2000 et Lisi *et al*., 2010). Among the registry studies specifying the frequency of occurrence of cardiac malformations after exposure *in utero* to carbamazepine monotherapy, a frequency of cardiac malformations between 0.3 and 1.6% is reported depending on the registers, counting between 703 and 1,657 pregnancies exposed to carbamazepine alone (Wide *et al*., 2004 and Kallen *et al*., 2013; Artama *et al*., 2005; Tomson *et al*., 2011; Hernandez-Diaz *et al*., 2012 and Campbell *et al*., 2014). It should be noted that the Kerala Epilepsy and Pregnancy Register reports a very high frequency of cardiac malformations among children exposed *in utero* to carbamazepine (6.3%), but this is to be placed in parallel with the rate observed in children not exposed to antiepileptics (8%) (Thomas *et al*., 2008). By compiling the data of 8 prospective studies of 2,680 pregnancies exposed to carbamazepine monotherapy, Jentink *et al*., 2010 report a statistically-significant increased risk of anomalous pulmonary venous return (p < 0.001). Among the studies comparing or making a parallel with the frequency of occurrence of cardiac malformations between the various

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antiepileptics, a lower frequency is observed after exposure *in utero* to carbamazepine, compared to valproate, without the difference being statistically-significant in the study having performed a statistical analysis (Campbell *et al.*, 2014). In contrast, an increased risk seems to come out among children exposed *in utero* to carbamazepine compared to lamotrigine, but no statistical analysis is performed by the authors (Tomson *et al.*, 2011). Finally, in the North American register, Hernandez-Diaz *et al.*, 2012 do not find an increased risk of cardiac malformations compared to a non-exposed external control group. Therefore, in the current state of knowledge, an increased risk of cardiac malformations among children exposed *in utero* to carbamazepine is described by certain studies, but is not found by others. Two of the 3 larger registers agree with the increased risk of cardiac malformations in children exposed *in utero* to carbamazepine. This risk is therefore to be taken into consideration.

♦ - Data currently available also describe an increased risk of oral clefts (Hernandez-Diaz *et al.*, 2007; Puho *et al.*, 2007; Lisi *et al.*, 2010; Gilboa *et al.*, 2011, ANSM/CNAM 2017), of hypospadias (Jentink *et al.*, 2010), of facial dysmorphia, of microcephalia, and of hypoplasia of the fingers (Jones *et al.*, 1989; Nulman *et al.*, 1997; Dean *et al.*, 2002; Mawer *et al.*, 2010) after exposure *in utero* to carbamazepine monotherapy. Other types of malformations have also been described, but occasionally.

Dose-effect relationship

Data currently available agree with a dose-effect relationship, with a particularly high risk of malformations with doses higher than or equal to 1,000 mg/day (Tomson *et al.*, 2011 and Campbell *et al.*, 2014). In so much, no dose without effect could be identified.

NEURODEVELOPMENTAL RISK

a) DQ and IQ scores

Pre-school children

The studies available in pre-school children exposed *in utero* to carbamazepine monotherapy do not show a statistically-significant reduction in overall DQ compared to children born to non-epileptic mothers (Scolnick *et al.*, 1994; Wide *et al.*, 2000 and Bromley *et al.*, 2010). The meta-analysis by Bromley *et al.*, 2014 finds a non-statistically-significant difference in DQ of -2.00 [-6.44; 2.44] (including the study using the Griffiths scales, namely Bromley *et al.*, 2010) and a statistically-significant difference of -5.58 [-10.83; -0.34] (including studies having used the Bayley scales: Ornoy *et al.*, 1996; Rovet *et al.*, 1995 and Hattig *et al.*, 1987). It should be noted that the study by Ornoy *et al.*, 1996 provides the cognitive DQ and psychomotor DQ separately (without providing the overall score) and that the authors of the meta-analysis included the cognitive DQ scores.

By comparison with children born to untreated epileptic mothers, the study available does not show a statistically-significant reduction in overall DQ in pre-school children exposed *in utero* to carbamazepine (with a 6-point reduction, close to statistical significance (p = 0.1); Bromley *et al.*, 2010). Nevertheless, on the basis of this study, the meta-analysis by Bromley *et al.*, 2014 finds a significant difference in DQ of -6.00 [-11.35; -0.65]. It should be noted that these results come from the Griffiths scales (Wide *et al.*, 2000 and Bromley *et al.*, 2010) or Bayley scales (Scolnick *et al.*, 1994); based on a limited number of exposed pregnancies (35; 48 and 36 respectively) and the study by Wide *et al.*, 2000 does not take the relevant maternal parameters into account. In contrast, the studies by Scolnick *et al.*, 1994 and by Bromley *et al.*, 2010 take account of the relevant maternal parameters, such as socio-economic status, IQ (and mother's age, parity and gravidity for Scolnick *et al.*, 1994).

By comparison with the other antiepileptics, the DQ of children exposed *in utero* to carbamazepine does not differ statistically from that of children exposed to phenytoin (Wide *et al.*, 2000 and Meador *et al.*, 2009), to lamotrigine (Meador *et al.*, 2009 and Bromley *et al.*, 2010), with a difference of -1.62 [-5.44; 2.21] by compiling the 2 studies (Bromley *et al.*, 2014). Also, the DQ of the children exposed *in utero* to carbamazepine are statistically higher than those of the children exposed *in utero* to valproate (Meador *et al.*, 2009 and Bromley *et al.*, 2010).

In addition, the 2 studies reporting the results of the cognitive DQ and psychomotor DQ separately (Bayley scales), Ornoy *et al.*, 1996 report a statistically-significant reduction in cognitive DQ in children exposed *in utero* to carbamazepine compared to the children born to non-epileptic mothers (100.3 (15.0) *versus* 112.4 (4.0)), which is not found by the study by Thomas *et al.*, 2008 by comparison with untreated epileptic women. It should be noted that this study does not take the relevant maternal parameters into account. With the same limit, the authors of this study report a statistically higher motor DQ in children exposed *in utero* to carbamazepine compared to the children exposed *in utero* to valproate. Finally, the study by Meador *et al.*, 2009 adjusting on the relevant confounding factors, seems to show (without any statistical analyses being performed) that at the age of 2 years, the children exposed *in utero* to carbamazepine have a lower verbal IQ than that of children exposed to lamotrigine or phenytoin, but higher than those exposed to valproate. A non-statistically significant reduction in linguistic competence is reported among the children exposed to carbamazepine (n = 36) by Scolnick *et al.*, 1994 by comparison with children born to non-epileptic mothers (n = 36).

School-age children

The studies currently available do not report a statistically significant difference in overall IQ between the children exposed *in utero* to carbamazepine and the children born to non-epileptic mothers (Wide *et al.*, 2002; Gaily *et al.*, 2004; Thomas *et al.*, 2007 and Baker *et al.*, 2015) or in the expected score (Nadebaum *et al.*, 2011). It should be noted that these

results are based on a small number of exposed pregnancies (35; 86; 14; 50 and 34 respectively) and that these studies take the mother's level of education into account, but that the only study published by Baker *et al.*, 2015 also adjusts on the maternal IQ, whereas Nadebaum *et al.*, 2011 do not report a difference between maternal IQ (in the carbamazepine group) and the IQ expected in the general population. The study by Titze *et al.*, 2008 is not examined here as it does not differentiate between exposure (n = 6) in mono- or polytherapy. In the same way, no statistically-significant difference is seen in overall IQ after prenatal exposure to carbamazepine compared to the children born to untreated epileptic mothers (Gaily *et al.*, 2004; Eriksson *et al.*, 2005 and Thomas *et al.*, 2007). Nevertheless, in these studies, the comparison with this type of control group (untreated epileptic mothers) does not take the relevant maternal parameters into account. By comparison with the other antiepileptics, Meador *et al.*, 2013 adjusting on the relevant confounding factors, do not show a statistically-significant difference between the overall IQ of the children exposed *in utero* to carbamazepine (n = 61) and that of the children exposed to phenytoin or to lamotrigine. Also, in the same study, the overall IQ of the children exposed *in utero* to carbamazepine is statistically higher (by 8 points) than that of children exposed *in utero* to valproate (Meador *et al.*, 2013). Thomas *et al.*, 2007 and Gopinath *et al.*, 2015 do not report a difference in overall IQ by comparison with children born to mothers treated with antiepileptic monotherapies other than carbamazepine, but without taking the relevant maternal parameters into account.

In addition, among the studies reporting verbal IQ and non-verbal IQ separately, the 2 studies taking the mother's level of education into account (Wide *et al.*, 2002; Gaily *et al.*, 2004) do not show a statistically-significant difference between the children exposed *in utero* to carbamazepine (n = 35 and n = 86) and the children born to non-epileptic mothers (n = 66 and n = 141). In the same way, Nadebaum *et al.*, 2011 (mother's IQ in the treated group not different from that expected in the general population) do not show a difference in verbal IQ and non-verbal IQ among the children in the carbamazepine group (n = 34) compared to the scores expected in the general population. In contrast, in a study of the same size, but also taking the mother's IQ into account Baker *et al.*, 2015, report a statistically-significant reduction in verbal IQ among the children exposed *in utero* to carbamazepine (n = 50) compared to the children born to non-epileptic mothers (n = 213), whereas the non-verbal IQ and spatial IQ are not statistically different. Finally, the study by Meador *et al.*, 2013, adjusting on the relevant confounding factors, shows that at the age of 6 years, the verbal IQ is no longer lower than the non-verbal IQ (104 (102 - 107) *versus* 104 (102 - 107)) and is statistically higher (by 7 points) than that of children exposed *in utero* to valproate. In the same way, the retrospective study conducted by Adab *et al.*, 2004 reports a statistically higher verbal IQ score among the children born to mothers treated with carbamazepine compared to those born to mothers treated with valproate (difference of around 10 points). Via a linguistic competence

test, Nadebaum *et al.*, 2011 do not show a statistical difference between the children exposed *in utero* to carbamazepine and the expected scores (p = 0.73) or the scores resulting in the children exposed *in utero* to valproate (p = 0.122).

Conclusion on the DQ and IQ scores:

In the current state of knowledge, the risk of cognitive disorders after exposure *in utero* to carbamazepine cannot be ruled out, but the impact on the IQ seems lower in any case than that of valproate. It is necessary to emphasise that this comparator (valproate) is not satisfactory as it is necessary to determine the neurodevelopmental outcome of the children exposed *in utero* to carbamazepine compared to the children born to untreated epileptic mothers or treated with antiepileptics other than valproate (and not only compared to valproate for which it is confirmed that it induces neurodevelopmental disorders in children exposed *in utero*).

b) Developmental delay (DQ or IQ scores < values considered) and learning disorders

Pre-school children

The studies available among pre-school children show that, by comparison with children born to non-epileptic mothers, the children exposed *in utero* to carbamazepine monotherapy have a higher frequency of developmental delay (DQ ≤ 84) (16% *versus* 8% according to Bromley *et al.*, 2010; 8% *versus* 3% according to Scolnick *et al.*, 1994 and 20% *versus* 5% according to Cummings *et al.*, 2011). This increased risk only reaches statistical significance in the study by Cummings *et al.*, 2011, with an ORa = 7.7 (1.4 – 43.1), by adjustment on the parameters influencing the child's IQ (but not the mother's IQ, unlike the other 2 studies). Nevertheless, the result from the study by Bromley *et al.*, 2010 is close to statistical significance (p = 0.074). By comparison with the other antiepileptics, Meador *et al.*, 2009 show an increased risk of disorders (DQ/IQ ≤ 84) among the children exposed *in utero* to carbamazepine (15/73; 20%) compared to those exposed to lamotrigine (10/84; 12%) but lower than that observed among the children born to mothers treated with phenytoin (15/48; 31%) or valproate (20/53; 37%). This last point is also observed in the Australian study, in which the estimated risk reported among the children exposed *in utero* to valproate (ORa = 26.1 (4.9 – 139)) is more than 3 times higher than that calculated for carbamazepine (ORa = 7.7 (1.4 – 43.1)) (Cummings *et al.*, 2011). This is also observed in the study by Bromley *et al.*, 2010 in which prenatal exposure to valproate leads to a statistically-significant increase in risk.

Also, in the study by Thomas *et al.*, 2008, not taking into account the maternal parameters but differentiating the cognitive DQ and motor DQ scores, the authors do not show a statistically-significant difference in developmental delay (motor DQ < 84 or cognitive DQ < 84) between the children exposed *in utero* to carbamazepine, to valproate, to phenobarbital or to phenytoin. In contrast, in the study by Bromley *et al.*, 2010 adjusting on the relevant confounding

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factors and by comparison with non-epileptic women, a statistically-significant delay (score ≤ 84) is shown in 2 areas of the Griffiths scales (motricity and eye-hand integration), but not in the other 3 areas (interpersonal skills/autonomy, performance and speech).

School-age children

◆ IQ score < values considered

The increased frequency of delay (not reaching statistical significance) observed among pre-school children exposed *in utero* to carbamazepine in the study by the "Liverpool and Manchester neurodevelopment group" is found among children age 6, with an RRa = 3.5 (1.1 − 10.2) by comparison with non-epileptic women and after adjustment on the relevant confounding factors (Baker *et al*., 2015). This is not found in the Australian study with respect to the frequencies expected in the general population (Nadebaum *et al*., 2011a, b).

By comparison with the other antiepileptics, the study by Meador *et al*., 2013 shows an increased risk of disorders (IQ ≤ 84) among the children exposed *in utero* to carbamazepine (5/61; 8 %) compared to those exposed to lamotrigine (2/74; 5 %) or phenytoin (2/40; 3%) but lower than that observed among the children born to mothers treated with valproate (8/49; 16 %).

It should be noted that the results above come from prospective cohorts taking the relevant maternal parameters into account (especially mother's level of education and IQ), but are based on a small number of exposed pregnancies (50; 34 and 61 respectively) (Baker *et al*., 2015; Nadebaum *et al*., 2011a, b and Meador *et al*., 2013).

Among the retrospective studies, the study by Vinten *et al*., 2005 does not show an increased risk of presenting with a verbal IQ of < 69 in the carbamazepine group compared to the untreated group (4/52 (7.7%) *versus* 6/80 (7.5%)) and reports a statistically higher frequency among the children exposed to valproate prenatally compared to those exposed to carbamazepine (9/41 (22%) *versus* 4/52 (7.7%)).

◆ Delayed acquisition / underachievement

Two studies report high rates of delayed acquisition in children exposed *in utero* to carbamazepine (22% delayed speech acquisition and/or motricity according to Dean *et al*., 2002; 30% psychomotor delays (delay, private tutoring, dependence) according to Mawer *et al*., 2002). It should be noted that these studies do not take the maternal parameters into account. The study with the most robust methodology, but covering a small number of children age 6 (n = 50) reports a non-statistically significant 3-fold increase in private tutoring among children exposed *in utero* to carbamazepine compared to the children born to non-epileptic mothers (Baker *et al*., 2015). Finally, in a Swedish study conducted among 16-year-old children, prenatal exposure to carbamazepine is not related to an increased risk in failure at sports, mathematics, English and Swedish, but is

related to a reduction in the proportion of children earning their diploma with excellence (for 3 of the 4 subjects studied, namely mathematics, English and Swedish) by comparison with children born to non-epileptic mothers or to children exposed *in utero* to phenytoin (Forsberg *et al*., 2011).

c) Attention deficit disorder with or without hyperactivity

Data currently available on attention deficit disorder, with or without hyperactivity, among children born to mothers exposed to carbamazepine are limited in terms of numbers (less than one hundred pregnancies) and methodology (composite questionnaires; frequency of children at risk of presenting with an attention deficit disorder with or without hyperactivity compared to the frequency of children presenting with an attention deficit disorder with or without hyperactivity; small numbers; etc.), contradictory, without clinical diagnosis (use of behavioural scales) concern children of an age younger (1.5, 3 and 6 years) than the age of onset of symptoms and do not necessarily study all subtypes (Van Der Pol *et al*., 1991; Veiby *et al*., 2013; Cohen *et al*., 2011 and 2013). Therefore, in the current state of knowledge, it is not possible to come to a conclusion on this risk.

d) Autism Spectrum Disorder (ASD)

The most robust study from a methodological (number of children, acknowledgement of relevant confounding factors) but retrospective standpoint, does not report a statistically-significant difference in the risk of pervasive developmental disorders (PDD) and infantile autism in the 386 children born to mothers treated with carbamazepine, with immediate risks of 1.0 (0.4 - 2.8) and 1.4 (0.4 - 5.8) respectively (Christensen *et al*., 2013). Data from the Australian prospective pregnancy register report 1 case of a child presenting with a score higher than 30, in favour of diagnosis of autism, on the CARS (Childhood autism rating score) and 1 case of a child with a borderline score (27-29), possibly suggesting a non-specific PDD, on the CARS (Childhood autism rating score), among the 34 children exposed *in utero* to carbamazepine monotherapy and blind-assessed between 6 and 8 years (Wood *et al*., 2015). The authors do not report a statistically-significant difference in the CARS score higher than 27 between the carbamazepine group (5.9%) and the group of children born to women treated with the other antiepileptics (valproate, polytherapy, other monotherapies; 9/71 (12.7%)). A smaller study of lesser methodological quality (including limits such as early age of the children studied, the absence of clinical diagnosis, use of a non-validated questionnaire, compiled for the study on the basis of items extracted from several development scales and screening tools in the general population), does not show an increase in the risk of autistic traits (via the Autism check-list) at 1.5 years (n = 41), however the authors report a non-statistically significant increase in autistic traits at 1.5 years (1/41; 2.9%), and 3 years (1/31; 3.4%) compared to the children born to non-epileptic mothers with a frequency of 0.9% at 1.5 years (i.e. OR = 3.3 (0.5 − 24.8)) of 1.5% at 3 years (i.e. OR = 2.5 (0.8-15.8)). It should be noted that the data relating to the risk of autistic traits only concerns 1 case at each age studied. Nevertheless,

the Scottish retrospective studies published by Dean *et al.*, 2002 and Rasalam *et al.*, 2005 agree with an increased risk. These studies mainly concern the same cohort (study conducted in the same hospital and during overlapping periods), one only investigating autism spectrum disorders (Rasalam *et al.*, 2005) and the second a set of developmental disorders (autism, ASD, Asperger or attention deficit and hyperactivity disorder (ADHD)) (Dean *et al.*, 2002). Rasalam *et al.*, 2005 report 2 cases of PDD among the 80 children exposed *in utero* to carbamazepine (2.5% (0 – 6%)) and report a rate of 0.25% (0.17 - 0.33) in the general population in the United Kingdom, but do not perform a statistical analysis (no control group specific to the study). In the study by Dean *et al.*, 2002 performing a pooled analysis of a set of developmental disorders (autism, ASD, Asperger or ADHD) established on the basis of medical records, the authors report an increased risk in the children exposed *in utero* to carbamazepine (10/70; 14.5%), by comparison with a control group of non-exposed children from the same mothers (2/38; 5.2%), which naturally makes it possible to control the potential confounding factors such as the social environment and the intellectual quotient and mother's level of education.

In the 2018 study conducted by ANSM and CNAM, exposure to carbamazepine appears to be associated with an increased risk of "psychological developmental disorders" and "behavioral and emotional disorders that usually appear during childhood and childhood adolescence ". However, these associations do not persist when the analysis is restricted to children born to mothers without an identified psychiatric illness.

Therefore, the data currently available on the risk of PDD or ASD among children exposed *in utero* to carbamazepine are contradictory and insufficient to be able to come to a final conclusion, and additional epidemiological studies would be necessary to confirm or invalidate the results.

e) Specific domains

Data currently available concerning impairment of the specific domains (mnestic, executive and adaptive functions, motricity, aggressive behaviour, social skills) among the children exposed *in utero* to carbamazepine are contradictory, insufficient, methodologically little robust for some (composite scale subscore, comparison to valproate and/or no administration of the questionnaires to both parents and teachers, etc.), based on small numbers, which makes interpretation of the results difficult and which means a conclusion cannot be come to (Thomas *et al.*, 2008; Mc Vearry *et al.*, 2009; Bromley *et al.*, 2010; Cohen *et al.*, 2011 and 2013; Veiby *et al.*, 2013; Meador *et al.*, 2013; Deshmukh *et al.*, 2016).

f) Conclusions on the neurodevelopmental risk

In the current state of knowledge, the risk of neurodevelopmental disorders (cognitive and/or behavioural) after exposure *in utero* to carbamazepine cannot be ruled out. If, after re-assessment, treatment is required, this risk is to be considered in the choice of treatment and should be taken into account for follow-up of the child in the event of exposure during the pregnancy.

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ESLICARBAZEPINE

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.
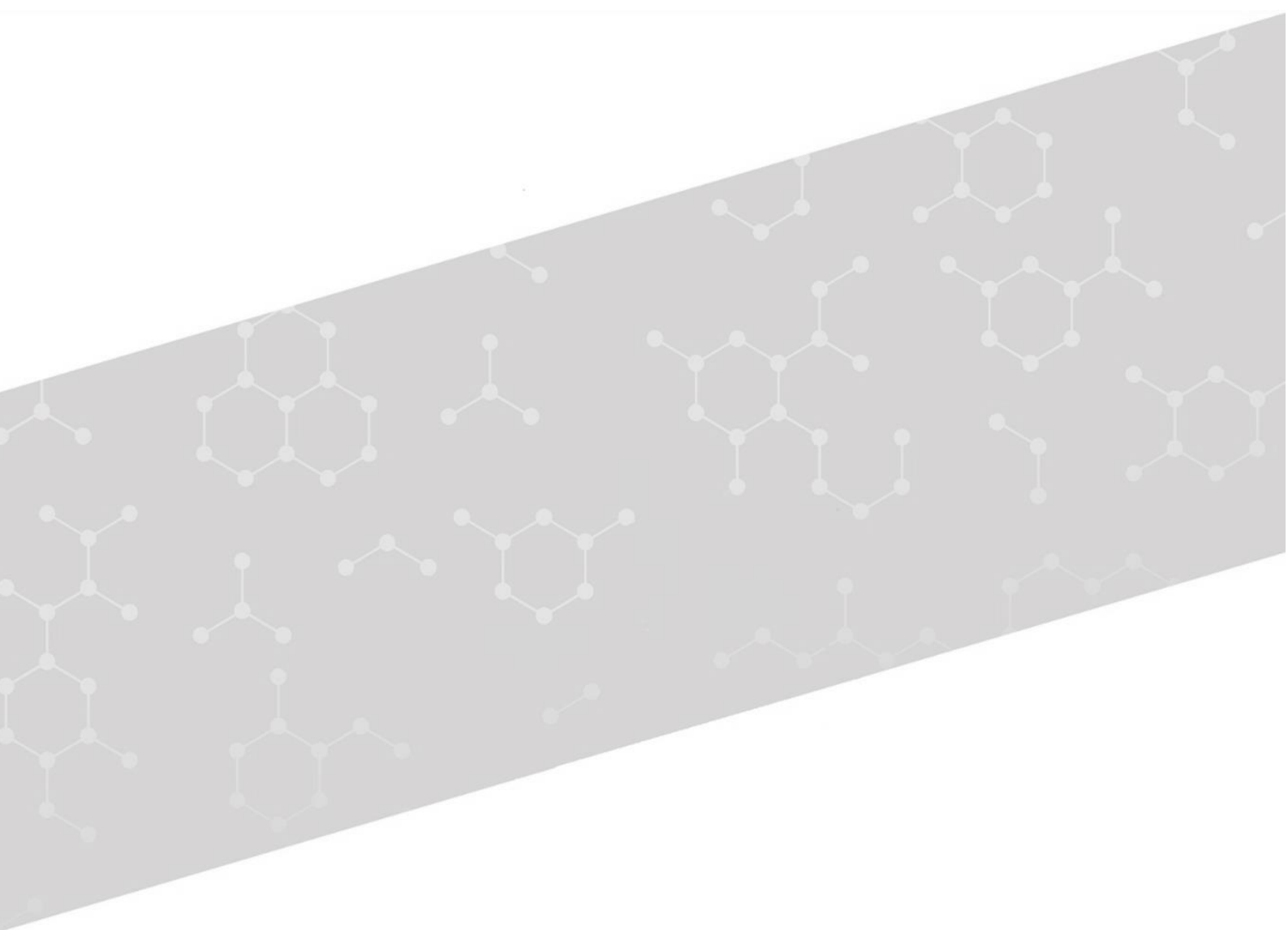
MALFORMATION RISK

Data in animals

Animal data mainly covers fertility and are fairly discordant concerning the malformation and/or foetotoxic risk. It would be desirable for the pharmaceutical company to revise the data. Nevertheless, the current SPC mention teratogenicity in mice (increase in the overall incidence of skeletal and major malformations).

Clinical data

The data are almost non-existent concerning eslicarbazepine and pregnancy: no bibliographic data and only 10 pregnancies exposed in monotherapy and the outcome of which is known (one case from Vigilyse® and 9 from the pharmaceutical company). The data collected prospectively report 1 case of miscarriage, 1 abortion (no details) and 2 normal births. The data collected prospectively report 2 cases of miscarriage, 2 abortions (no details), 1 normal birth and birth of 1 child with a defect (congenital dislocation of the knee). These data cannot be used to conclude as to the potential risk concerning use of eslicarbazepine during the pregnancy.

NEURODEVELOPMENTAL RISK

To date, the data relating to the neurodevelopmental risk further to exposure *in utero* to eslicarbazepine alone are non-existent or almost non-existent, not enabling a conclusion.

ETHOSUXIMIDE

INTERACTIONS WITH HORMONAL CONTRACEPTION

Data relating to the interactions with hormonal contraceptives are missing.

MALFORMATION RISK

Data in animals

Animal data have shown a teratogenic effect from ethosuximide (cerebral, skeletal and visceral malformations).

Clinical data

The data available from literature and from spontaneous reports are insufficient to be able to accurately assess the malformation risk from ethosuximide, often used in polytherapy. Data from literature on this molecule are also sometimes relatively old. We counted 76 pregnancies exposed in monotherapy in literature (Kuhnz *et al.*, 1984; Bertollini *et al.*, 1987; Samrén *et al.*, 1997; Samrén *et al.*, 1999; Morrow *et al.*, 2006; Tomson *et al.*, 2018; Kallen *et al.*, 2013; Vajda *et al.*, 2014) with 3 cases of malformations reported: in 2 brothers, with certain similar defects of the nose (Kuhnz *et al.*, 1984) and one other case without information (Samrén *et al.*, 1997)). Among the 72 pregnancies exposed in monotherapy, 30 were collected prospectively, with 2 cases of malformations (case of the 2 brothers reported above). The outcome in these studies is not specified, since most often, only the births are reported. Data from the spontaneous reports cover 10 pregnancies exposed in monotherapy and followed-up prospectively: 5 from Terappel®, with exposure in the 1st trimester and 5 from the pharmaceutical company (for the latter, exposure in the 1st trimester is not always clearly established, except at least in one women who discontinued ethosuximide at 10 WA and switched to diazepam), with malformations in this case and not in the others. In conclusion, the data from literature and spontaneous reports are very few, with 32 cases of pregnancies followed-up prospectively, exposed to ethosuximide monotherapy in the 1st trimester.

NEURODEVELOPMENTAL RISK

In the current state of knowledge, the data relating to the neurodevelopmental risk further to exposure *in utero* to ethosuximide alone are almost non-existent, not enabling a conclusion.

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FELBAMATE

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Data in animals

Studies conducted in animals (rats and rabbits) did not reveal a teratogenic effect from felbamate at doses ranging up to 13.9 times and 4.2 times the daily human dose respectively, calculated on the bodyweight.

Clinical data

Current data from literature only cover a very small number of patients: 13 of which only 3 exposed in monotherapy (the conditions of exposure are not known for the 10 others) (Morrell *et al.*, 1996; Tomson *et al.*, 2018). Spontaneous report data (pharmaceutical company and Vigilyse®) count 9 cases of pregnancies exposed in monotherapy, of which 4 pregnancies were recorded retrospectively, and no information is available for the 5 others on the method of collection. No conclusion as to the malformation risk during exposure *in utero* to felbamate can be issued from this data.

NEURODEVELOPMENTAL RISK

To date, the data relating to the neurodevelopmental risk further to exposure *in utero* to felbamate alone are almost non-existent, not enabling a conclusion.

HAEMATOLOGICAL AND HEPATIC TOXICITY

In the light of the toxicity profile of felbamate, if, after re-assessment, treatment is required, the potential risk of haematological toxicity and hepatotoxicity is to be considered in the choice of treatment and should be taken into account for follow-up of the child in the event of exposure during the pregnancy.

GABAPENTIN

INTERACTIONS WITH HORMONAL CONTRACEPTION

Concomitant administration of gabapentin and oral contraceptives containing norethindrone and/or ethinylestradiol does not modify the pharmacokinetic parameters in steady state of either of the products.

MALFORMATION RISK

Data in animals

In mice and rats, gabapentin is not teratogenic at doses 1 to 4 times the human dose. Nevertheless, delayed ossification has been observed at different levels (skull, vertebrae, limbs). Hydronephrosis and hydroureter have been reported in rats exposed to gabapentin in the prenatal phase. These effects were observed at maternotoxic doses. An embryolethal effect was observed in rabbits.

Clinical data

Data currently available in literature concerning exposure to gabapentin in monotherapy during pregnancy are limited (Wilton et Shakir, 2002; Montouris, 2003; Morrow *et al*., 2006; Hernandez-Diaz *et al*., 2012; Guttuso *et al*., 2010; Fujii *et al*., 2013; Kallen *et al*., 2013; Fuzier *et al*., 2013; Vajda *et al*., 2014; Veiby *et al*., 2014; Tomson *et al*., 2018). Published data counts fewer than 300 pregnancies exposed in monotherapy in the 1st trimester and collected prospectively (~ 250 pregnancies). The 2 studies including the higher number of pregnancies exposed to gabapentin monotherapy (n = 145 prospective register; n = 119 by retrospective register cross-referencing) do not report an increase in the risk of congenital malformation, with malformation rates of 0.7% (0.02 – 3.8) (Hernandez-Diaz *et al*., 2012) and 1.7% (Kallen *et al*., 2013). Moreover, study conducted in 2017 by ANSM and CNAM report that a risk of 26 major congenital malformations studied did not differ between the children born to mothers exposed to gabapentin in monotherapy (N=372) and children born to mothers not exposed during pregnancy. It should be noted that a high rate of prematurity is observed in children born to mothers treated with gabapentin registered in the EFEMERIS database (n = 21; 43% of premature births including 1 case of triplets). As this rate is based on a small number of births, without taking certain risk factors into account (indication, body mass index, obstetrical history, smoking, etc.), it is to be considered with caution, and cannot be used to come to a conclusion.

Among the malformations reported in scientific literature, without concomitant exposure to a substance known to be teratogenic, the defects reported are mainly renal (n = 2); cardiac (n = 2); gastrointestinal (n = 2) and central nervous system (n = 2) malformations. The proportions of central nervous system malformations and renal defects appear high compared to the other types of malformations. Nevertheless, in the light of the very small number of cases, the lack of detail on the risk factors, other than concomitant drug exposure (such as the mother's history, alcohol consumption, exposure to other substances, etc.) and the different methodologies used in the studies (prospective and retrospective data collection; different follow-up periods; etc.), these data must be considered with caution and cannot be used to make a comparison with the general population, or to conclude as to the malformative profile of gabapentin. However, as renal malformations were observed in animal studies, it appears necessary to draw the attention of healthcare professionals as to the possibility of this type of malformation.

NEURODEVELOPMENTAL RISK

Data from scientific literature relating to the neurodevelopmental risk further to exposure *in utero* to gabapentin alone are almost non-existent, not enabling a conclusion. In the study conducted in 2018 by ANSM and CNAM, exposure *in utero* to gabapentin does not appear to be associated to neurodevelopmental risk. However, these results should be interpreted with caution because of the limited number of cases among exposed children

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LACOSAMIDE

INTERACTIONS WITH HORMONAL CONTRACEPTION

In an interaction study, no clinically-significant interaction was observed between lacosamide and the oral contraceptives, ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicines were administered concomitantly.

MALFORMATION RISK

Data in animals

Studies in animals did not show teratogenic effects (in rats or rabbits) but demonstrated embryotoxicity at maternotoxic doses. Nevertheless, as the dose levels tested in animals are lower than the therapeutic doses used in humans, animal data are insufficient for characterising the embryofoetotoxic and teratogenic potential of lacosamide.

Overall frequency of malformations

Data currently available concerning exposure to lacosamide during pregnancy are very limited (Isojarvi *et al*., 2009; Hoeltzenbein *et al*., 2011; Tomson *et al*., 2018; spontaneous reports), with:

♦ around 46 pregnancies exposed in monotherapy at least during the 1st trimester:
  - Of which around 36 collected prospectively, among which no major malformations are reported (1 malformation of the pinna ranked as a minor malformation)
  - Of which 2 cases of malformation (among which 1 with a risk factor) reported among the 10 cases collected retrospectively
♦ around 120 pregnancies exposed in polytherapy at least once during the 1st trimester (around 90 collected prospectively and 30 retrospectively), with, for most of them, known risk factors and/or missing information, not making it possible to conclude as to the role of lacosamide.

Types of malformations

Among the malformations observed, the presence of risk factors (especially in terms of co-exposure) or the lack of information (on the malformations and/or co-exposure) for most of the cases does not make it possible to analyse or to identify a specific malformative profile from lacosamide.

Dose-effect relationship

No study concerning the relationship between the lacosamide dose and the risk of disorders in children exposed *in utero* has been identified for lacosamide.

NEURODEVELOPMENTAL RISK

In the current state of knowledge, the data relating to the neurodevelopmental risk further to exposure *in utero* to lacosamide alone are almost non-existent, not enabling a conclusion.

LAMOTRIGINE

INTERACTIONS WITH HORMONAL CONTRACEPTION

In a study conducted in 16 women receiving the combined pill, a 300 mg lamotrigine maintenance dose did not change ethinylestradiol concentrations. A moderate reduction in levonorgestrel concentrations lower than 20% was observed, which is within the bioequivalence range, along with variations in serum FSH and LH levels without an effect on ovulation. Nevertheless, by precaution, another contraceptive method should be used.

MALFORMATION RISK

Overall frequency of malformations

Therefore, according to studies currently available, the overall frequency of major malformations among children exposed *in utero* to lamotrigine monotherapy varies between 2.0% and 3.65%. This variability can be related to the differences in methodology between the studies, at the doses administered, etc. It should be noted that the highest frequency (3.65%) is reported in the study with the lowest numbers (n = 356) (Vajda *et al*., 2016). In the 4 registers having collected the largest number of pregnancies exposed to lamotrigine monotherapy (> 1,000 pregnancies in each register), the overall frequency of malformations is between 2 and 3%, which is on a par with the overall frequency of malformations observed in the general population, namely 2-3% (Tomson *et al*., 2018; Cunnington *et al*., 2011; Hernandez-Diaz *et al*., 2012; Campbell *et al*., 2014). This is confirmed by the meta-analyses conducted by Weston *et al*., 2016 who report that the children exposed *in utero* to lamotrigine have a mean malformation rate of 2.31% (1.87% – 2.78% n = 4195), a rate which does not differ statistically from that of the non-exposed control groups (non-epileptic or epileptic).

In addition, none of the 4 studies establishing a comparison between the children born to mothers exposed to lamotrigine monotherapy and those born to untreated, non-epileptic mothers, report a statistically significant difference in risk (Meador *et al*., 2008; Hernandez-Diaz *et al*., 2012; Kallen *et al*., 2013 and Veiby *et al*., 2014). Data from the Australian register and from the United Kingdom Register lead to a similar conclusion, by comparison with a group of untreated epileptic mothers (Vajda *et al*., 2016 and Campbell *et al*., 2014). Finally, among the registers comparing the frequencies of malformations for the various antiepileptics, the overall frequency of malformations after exposure *in utero* to lamotrigine is statistically lower than that with valproate, phenobarbital, topiramate and/or carbamazepine, according to the registers (Tomson *et al*., 2018; Hernandez-Diaz *et al*., 2012; Campbell *et al*., 2014).

Types of malformations

To date, the possibility of an increased risk of oral clefts has been mentioned in one study (Holmes *et al*., 2006 and 2008), and the absence of confirmation in several other studies, including a case control study, means this risk cannot be applied to lamotrigine (Hunt *et al*., 2009; Kallen *et al*., 2013; Veiby *et al*., 2014; Dolk *et al*., 2016). Also, potential signals have been identified for certain types of malformations, without them being observed to date in the other studies available, despite the numerous data available: club foot (mentioned in one study (Dolk *et al*., 2016), but not found in an independent study by the same team (Dolk *et al*., 2016) and in the study by Kallen *et al*., 2013), stenosis of the upper airways (mentioned in one study (Dolk *et al*., 2016) having performed a large number of statistical comparisons, on a small number of cases (n = 5) and not identified in the other studies), cardiopathy (observed in the ANSM / CNAM study conducted in 2017, was not reported in other studies).

Dose-effect relationship

An increased risk of malformation for the highest doses is mentioned in a study conducted by Tomson *et al*., 2018 (from 325 mg/d), but is not found in 3 other studies of similar magnitude (Cunnington *et al*., 2011 ; Hernández‑Díaz *et al*., 2012 et Campbell *et al*., 2014), including one considering the same dose threshold. Nevertheless, additional data are necessary to come to a final conclusion.

Conclusion on the malformation risk

Therefore, in the current state of knowledge, follow-up of a very large number of pregnant women exposed to lamotrigine monotherapy in the 1st trimester of pregnancy (> 5,000 pregnancy outcomes) did not show an increase in the overall risk of major malformations. Nevertheless, monitoring of the malformation risk must be continued on the whole, and in particular for the types of malformations for which a potential signal was identified in certain studies, and which require additional research.

NEURODEVELOPMENTAL RISK

a) DQ and IQ scores

Pre-school children

The studies available concerning the DQ (in preschool children) show the absence of relationship between prenatal exposure to lamotrigine and the DQ score, in comparison:

- ◆ to the children born to non-epileptic women (Bromley *et al*., 2010), difference of -1.00 [-5.75; 3.75] (Bromley *et al*., 2014)
- ◆ to the children born to untreated epileptic women (Bromley *et al*., 2010), with a difference of -5.00 [-10.70; 0.70] (Bromley *et al*., 2014)

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- to the children exposed *in utero* to carbamazepine alone (Meador *et al*., 2009), difference of -3.00 [-9.29; 3.29] (Bromley *et al*., 2014)
- to the children exposed *in utero* to phenytoin alone (Meador *et al*., 2009), difference of -7.00 [-14.48; 0.48] (Bromley *et al*., 2014).

Also, Meador *et al*., 2009 observe statistically higher DQ among the children exposed *in utero* to lamotrigine alone compared to the children exposed *in utero* to the valproate alone (VPA *versus* LTG: -12.00 [-20.31; - 3.69]) (Bromley *et al*., 2014).

School-age children

In the same way, studies concerning the IQ (school-age children) do not show a statistically significant difference in IQ between the children exposed *in utero* to lamotrigine alone and:

- the children born to non-epileptic mothers (Baker *et al*., 2015),
- the children born to untreated epileptic mothers (Baker *et al*., 2015),
- the children born to non-exposed, non-epileptic mothers (Rihtman *et al*., 2013).
- the children exposed *in utero* to carbamazepine or phenytoin (Meador *et al*., 2013 and Baker *et al*., 2015).

In addition, by compiling the studies by Meador *et al*., 2013 and Bromey *et al*., 2010 (the most recent results of which were published by Baker *et al*., 2015), prenatal exposure to lamotrigine (n = 84) is related to IQ scores around 10 points higher than those observed among children exposed *in utero* to valproate (valproate *versus* lamotrigine: -10.80 [-14.42; - 7.17]) (Bromley *et al*., 2014). This difference is not found when comparing lamotrigine to carbamazepine or phenytoin (Meador *et al*., 2013 and Baker *et al*., 2015).

Conclusion on the DQ and IQ scores:

Therefore, the studies available do not show a statistically significant difference in DQ and IQ among the children exposed *in utero* to lamotrigine compared to the children born to non-epileptic mothers, untreated epileptic mothers or mothers treated with carbamazepine or phenytoin. Also, statistically higher DQ and IQ were reported in the children born to mothers treated with lamotrigine by comparison with the children born to mothers treated with valproate (Bromley *et al*., 2010; Meador *et al*., 2009; Meador *et al*., 2012; Meador *et al*., 2013; Bromley *et al*., 2014; Baker *et al*., 2015). Nevertheless, it should be noted that the number of children followed-up is small, since the data, which is based on 3 registers (Liverpool and Manchester, NEAD, Australian) and 1 prospective study (Israeli study), only cover around one hundred children (with some patients in both the studies by Bromley *et al*., 2010 and Meador *et al*., 2009; 2013).

Therefore, in the current state of knowledge, follow-up of a small number of children exposed *in utero* to lamotrigine monotherapy (~100) did not show an increased risk of a reduction in DQ or IQ. Nevertheless, the data are too few to be able to come to a final conclusion and additional epidemiological studies are necessary

b) Developmental delay (DQ or IQ scores < values considered) and learning disorders

Pre-school children

Studies on the frequency of developmental delay (DQ or IQ < values considered) among pre-school children exposed *in utero* to lamotrigine monotherapy show:

- the absence of difference compared with children born to non-epileptic mothers (15% *versus* 8% according to Bromley *et al*., 2010; and 3% *versus* 5% according to Cummings *et al*., 2011, i.e. an ORa = 1.1 (0.1 – 13.7), adjusted on the parameters influencing the child's IQ (except the mother's IQ according to Cummings *et al*., 2011)).
- a lower risk of delay (DQ/IQ<85) or identical risk (<70) compared to the children exposed *in utero* to carbamazepine (Meador *et al*., 2009 and Cummings *et al*., 2011)
- a lower risk of delay (DQ/IQ<85) or identical risk (<70) compared to the children exposed *in utero* to phenytoin (Meador *et al*., 2009 and Cummings *et al*., 2011)
- a lower risk of delay (DQ/IQ<85) or identical risk (<70) compared to the children exposed *in utero* to valproate (Meador *et al*., 2009, Cummings *et al*., 2011 et Bromley *et al*., 2010)).

School-age children

Studies on the frequency of developmental delay (IQ < values considered) among pre-school children exposed *in utero* to lamotrigine monotherapy show:

- no significant difference in the frequency of occurrence of delays (IQ ≤ 84) or in use of private tutoring, by comparison with the children of non-epileptic women and after adjustment on relevant confounding factors (Baker *et al*., 2015).
- a lower risk of delay (IQ<85) or identical risk (<70) compared to those exposed to carbamazepine (Meador 2013) with an RR = 2.28 (0.63 – 8.22) for IQ < 85 (Bromley *et al*., 2014),
- a lower risk of delay (IQ<85) or identical risk (<70) compared to the children exposed to phenytoin (Meador *et al*., 2013),
- a lower risk of delay (IQ<85) or identical risk (<70) compared to those exposed to valproate (Meador *et al*., 2013) with an RR = 4.87 (1.50 – 15.78) for IQ < 85 (Bromley *et al*., 2014).
- the absence of delayed speech among the 9 children exposed to lamotrigine prenatally (Nadebaum *et al*., 2011a, b).

It should be noted that these results are based on a small number of exposed pregnancies to collected prospectively (30; 9 and 74 respectively) and that these studies take the relevant maternal parameters into account (especially the mother's

level of education and IQ) (Baker *et al.*, 2015; Nadebaum *et al.*, 2011a,b and Meador *et al.*, 2013).

Conclusion on developmental delay and learning disorders

Therefore, in the current state of knowledge, follow-up of a small number of children exposed *in utero* to lamotrigine monotherapy (~100) did not show an increased risk of developmental delay. In effect, the most robust studies in terms of the number of exposed pregnancies, in terms of relevant parameters and clinical diagnosis did not demonstrate developmental delay in the children exposed *in utero* to lamotrigine, evaluated up to the age of 6 years, or an increased need for private tutoring (Cummings *et al.*, 2011; Meador *et al.*, 2013; Bromley *et al.*, 2010; Nadebaum *et al.*, 2011a,b; Baker *et al.*, 2015). Nevertheless, the data are too few to be able to come to a final conclusion and additional epidemiological studies are necessary.

c) Attention deficit disorder with or without hyperactivity

Data currently available cannot be used to conclude on a significant risk of attention deficit disorder, with or without hyperactivity in children born to mothers exposed to lamotrigine. In effect, the data are limited in terms of numbers (around one hundred pregnancies) and methodology (composite questionnaires; frequency of children at risk of presenting with an attention deficit disorder with or without hyperactivity compared to the frequency of children presenting with an attention deficit disorder with or without hyperactivity; small numbers; without clinical diagnosis (use of behavioural scales) concern children of an age younger (1.5, 3 and 6 years) than the age of onset of symptoms and do not necessarily study all subtypes (Veiby *et al.*, 2013; Cohen *et al.*, 2011 et 2013 et Rihtman *et al.*, 2013). Therefore, in the current state of knowledge, it is not possible to come to a final conclusion on this risk.

d) Autism Spectrum Disorder (ASD)

The most robust study from a methodological standpoint in terms of number of children, acknowledgement of relevant confounding factors and clinical diagnosis, although retrospective, does not report a statistically-significant difference in the risk of PDD and infantile autism in the 647 children born to mothers treated with lamotrigine compared to the general population, with immediate risks of 1.7 (0.8 - 3.5) and 1.7 (0.5 - 5.2) respectively (Christensen *et al.*, 2013). Two smaller studies, of lesser methodological quality, demonstrate an increase in risk. In the Norwegian prospective cohort MoBA (Mother & Child Cohort Study) conducted over the study period 1999 – 2008, no anomalies, in the questionnaire battery, were seen in favour of impaired development at the age of 18 months, among the 65 children exposed *in utero* to lamotrigine, compared to the control group of children born to non-epileptic mothers (Veiby *et al.*, 2013). In contrast, at the age of 36 months, this study reports a statistically-significant increase in autistic traits among the 44 children exposed *in utero* to lamotrigine (4/44; 9.3%) compared to the children born to

untreated, non-epileptic mothers (n = 43571; 1.5%) i.e. An OR = 5.0 (1.7 – 14.4). It should be noted that in this study, no diagnostic assessments of autism took place, but autistic traits were estimated (symptoms suggesting autistic traits) from the responses to completed by the mothers; these questionnaires were not validated and are compiled in this study (combining 2 validated structured interviews as tools for screening symptoms suggestive of autistic traits usually conducted by a clinical assessor, which her were transformed into a questionnaire sent by post). Therefore, this study is to be considered with caution given the methodological bias (age of the children, absence of clinical diagnosis, non-validated questionnaire, compiled for the study on the basis of items extracted from several development scales and screening tools for the general population, with very small numbers). In the study by the "Liverpool and Manchester neurodevelopment group", the blinded assessment as to exposure to antiepileptics shows a non-statistically significant increase in the risk of neurodevelopmental disorders of the ASD type, attention deficit disorder with or without hyperactivity (ADHD) or dyspraxia (considered together as developmental disorders) among children age 6, exposed to lamotrigine. In effect, these disorders were observed in 2 of the 30 children exposed *in utero* to lamotrigine alone (6.7%) *versus* 1.9% (4/214) among the children born to untreated, non-epileptic mothers, i.e. an ORa = 4.06 (0.55 – 22.2), after adjustment on seizures during the pregnancy, the mother's IQ, the mother's age, socio-economic status, smoking, alcohol consumption, sex and gestational age at birth (Bromley *et al.*, 2013). Data from the Australian pregnancy register, do not report any cases of children with a score higher than or equal to 30 on the CARS (Childhood autism rating score) scale among a very small number of 9 children exposed *in utero* to lamotrigine monotherapy (Wood *et al.*, 2015). An unpublished study (cited by Bromley *et al.*, 2014) does not report any cases of ASD among 35 children exposed *in utero* to lamotrigine. Therefore, in the current state of knowledge, the data are too few to be able to come to a final conclusion and additional epidemiological studies are necessary to confirm or invalidate the results.

In addition, in the study conducted in 2018 by the ANSM and the CNAM, the risk of diagnosis of mental and behavior disorders among children exposed in utero to lamotrigine (main alternative to valproic acid) is 3 times lower compared to children exposed to valproic acid. Compared to unexposed children, exposure to lamotrigine appears to be associated with a global risk of diagnosis of mental and behavior disorders 1.6 times higher, particularly with an increased risk of having "mental retardation" and "psychological development disorder".

Importantly, these associations do not persist when the analysis is restricted to children born to mothers without an identified psychiatric illness, suggesting that the increased risk of neurodevelopmental disorders could be explained not by exposure to lamotrigine but rather by an effect of maternal psychiatric disease and / or its associated characteristics.

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e) Specific domains

Concerning motor, mnemonic, executive and adaptive functions, interpersonal skills, and speech, there are few data and the studies are sometimes little-robust, with small numbers, but do not make it possible to conclude, in the current state of knowledge, on a significant risk of impairment of these domains in the children exposed *in utero* to lamotrigine (Mc Vearry *et al.*, 2009; Bromley *et al.*, 2010; Cohen *et al.*, 2011 and 2013; Meador *et al.*, 2013; Rihtman *et al.*, 2013; Veiby *et al.*, 2013 and Deshmukh *et al.*, 2016). In conclusion, the data are currently too few to be able to come to a final conclusion and additional epidemiological studies are necessary.
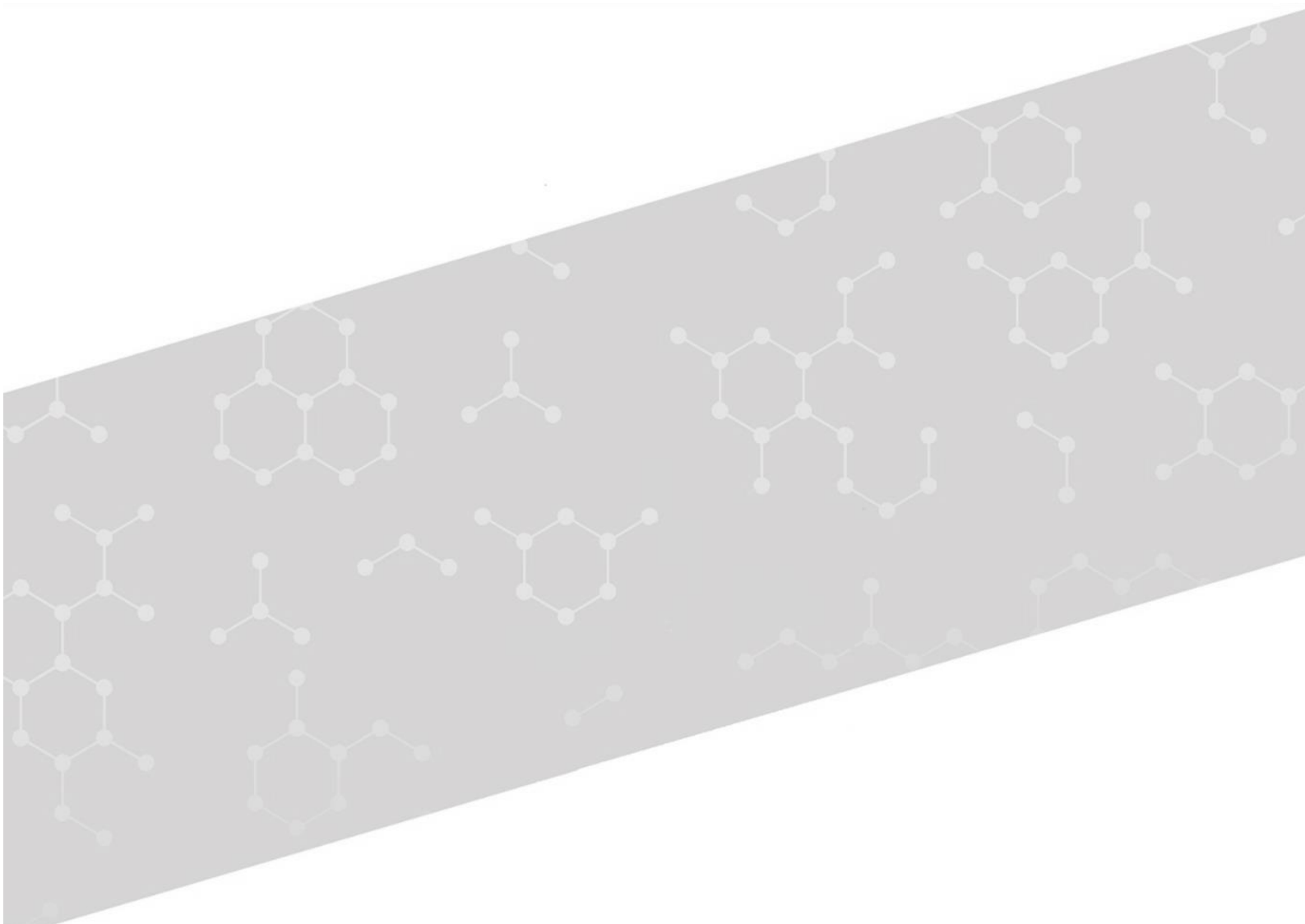
LEVETIRACETAM

INTERACTIONS WITH HORMONAL CONTRACEPTION

Levetiracetam at the dose of 1,000 mg per day did not change the pharmacokinetics of the oral contraceptives (ethinylestradiol and levonorgestrel); the endocrine parameters (luteinizing hormone and progesterone) were not affected.

MALFORMATION RISK

Data in animals

In rats, a slight reduction in foetal bodyweight along with an increase in the minor skeletal variations/defects was observed. In rabbits, a reduction in bodyweight and an increase in cardiovascular / skeletal defects were observed at the highest dose tested (maternotoxic dose).

Clinical data

To date, data from scientific literature covering the malformation risk after exposure *in utero* to levetiracetam do not highlight a substantial increase in the overall risk of malformations. In total, 1,500 patients were followed-up (data from literature, the main studies being Tomson *et al*., 2018; Hernandez-Diaz *et al*., 2012; Vajda *et al*., 2012; Mawhinney *et al*., 2013). According to the main studies, with good methodology, the malformation rate varies between 0.7 and 2.8%. This is confirmed by the meta-analyses conducted by Weston *et al*., 2016 who report that the children exposed *in utero* to levetiracetam have a mean malformation rate of 1.77% (0.98% – 2.79%) (n = 817), a rate which does not differ statistically from that of the non-exposed control groups (non-epileptic or epileptic). It should be noted that the data from the UCB register report a malformation rate of 9.4%. From this data, a statistically-significant increase in the risk of major malformations can be seen (RR = 2.8; 95% CI: 1.8-4.3) as in ventricular septum defects (RR = 3.0; 95% CI: 1.3-7.2) among the women exposed to levetiracetam monotherapy and during the first trimester (n = 247), compared to the population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Nevertheless, the results for this register are to be taken with caution as there is significant bias. For example, the data from the MACDP are older than that from UCB, the women exposed to the antiepileptics and their child are followed more closely than the general population (malformations better detected), also risk factors for cardiac malformations were not taken into account (such as alcohol, serotonin reuptake inhibitor antidepressants etc.). Finally, the North American register reviewed the data of the UCB register to look for an explanation

as to the high rate of malformations identified in the UCB register compared to the other registers. According to the authors of the North American register, there is essentially a difference on the definition of the malformations: 19 cases of malformation out of 46 were apparently not included in the North American register. They are cases of hereditary malformations, minor malformations, cases considered to be malformations (i.e.: nystagmus, torticollis) and absence of exposure at the time of organogenesis (formation of the target organ). Also, several cases are doubtful (lack of information). Out of the 6 cases of ventricular septum defect, 3 are believed to be excluded.

Regarding the risk of 26 major congenital malformations, a study conducted in 2017 by ANSM and CNAM report that there was no statistical difference between the children born to mothers exposed to levetiracetam in monotherapy (N = 594) and children born to mothers not exposed during pregnancy.

Conclusion on the malformation risk

Therefore, in the current state of knowledge, data from main studies with appropriate methodology, do not agree with an substantial increase in the overall risk of malformations compared to the frequency observed in the general population (which is 2-3%), and this on the basis of a high number of pregnancies exposed in monotherapy in the 1st trimester of pregnancy (> 1,000). Nevertheless, the malformation risk must continue to be monitored on the whole, and for different types of malformations.

NEURODEVELOPMENTAL RISK

The 4 articles published suggest that exposure *in utero* to levetiracetam does not significantly increase the risk of neurodevelopmental disorders in children (Shallcross *et al*., 2011; Shallcross *et al*., 2014; Arkilo *et al*., 2015; Bromley *et al*., 2016). Nevertheless, the data remain insufficient to be able to conclude. In effect, the numbers in these studies are very low for a low frequency risk studied. Study conducted in 2018 by ANSM and CNAM report an increased risk of having a consultation with an orthoptist (HR = 1.3 (1-1.7)) and with a psychiatrist (HR = 2 (1-4.1)) among children exposed to levetiracetam born to mothers without an identified psychiatric illness. However, these associations are at the limit of significance and no association with increased risk of diagnosis of mental and behavioral disorders was found.

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OXCARBAZEPINE

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Data in animals

Studies in animals have shown increases in the incidence of embryo mortality and mild antenatal and/or postnatal developmental delay at doses toxic for the mother. An increase in foetal malformations in rats was observed in one of the eight embryotoxicity studies carried out with oxcarbazepine or its pharmacologically-active metabolite (DMH) at a dose which was also toxic for the mother. The malformations observed in rats are craniofacial, cardiovascular and skeletal malformations.

Clinical data – Overall frequency of malformations

By examining the 4 largest studies in terms of the number of exposed pregnancies, namely Tomson *et al.*, 2011; Hernandez-Diaz *et al.*, 2012 (prospective studies) and Artama *et al.*, 2005 , Veiby *et al.*, 2014 (retrospective studies), the overall frequency of occurrence of major malformations among the children exposed *in utero* to oxcarbazepine monotherapy varies between 1% and 3.3%. Higher frequencies were reported in small prospective case series. These variabilities may be related to the different methodologies between the studies, to the small numbers, to the doses administered, etc. The overall frequency of malformations in the general population is 2-3%. According to the meta-analyses conducted by Weston *et al.*, 2016, the children exposed *in utero* to oxcarbazepine have a mean malformation rate of 2.39% (0.85% - 4.68%) (n = 238; 4 studies).

Also, no statistically significant difference in malformation after exposure *in utero* to oxcarbazepine is reported in the larger studies, by comparison with a control group of untreated, non-epileptic women (RR = 2.0 (0.5 – 7.4) and RR = 0.64 (0.10 - 4.61), according to the studies by Hernandez-Diaz *et al.*, 2012 and Veiby *et al.*, 2014) and of lamotrigine-treated epileptic women (RR = 1.1 (0.4 – 3.2) and 1.1 (0.5 – 2.7), according to the studies by Hernandez-Diaz *et al.*, 2012 and Tomson *et al.*, 2018). A non-statistically-significant increase in the malformation risk from oxcarbazepine compared to the general population is suggested in a study based on a small number of exposed pregnancies (n = 40; ORa = 2.27 (0.62 - 5.82)) (Kallen *et al.*, 2013). An increase risk of malformations among the children exposed *in utero* to oxcarbazepine compared to an untreated epileptic control group was only suggested in one study, only including 9 women exposed (Kaaja *et al.*, 2003), and was not confirmed in 2 other studies (OR = 0.36 (0.01 – 2.23) and RR =

1.8 (0.22 - 14.5), according to the studies by Artama *et al.*, 2005 and Vajda *et al.*, 2014). It should be noted that the numbers in these studies only confer them limited statistical power for detecting an increase in risk (broad confidence intervals). Finally, according to the meta-analyses conducted by Weston *et al.*, 2016, prenatal exposure to oxcarbazepine is not related to a statistically-significant increase (RR = 1.94 (0.53 - 7.15) compared to non-epileptic women; RR = 2.75 (0.53 - 14.43) compared to untreated epileptic women), however the data available are considerably fewer compared to older substances.

Clinical data – Type of malformations

The literature search did not find any studies specifically investigating the link between a specific type of malformation and exposure *in utero* to oxcarbazepine monotherapy. Among the studies available describing the malformations observed after exposure *in utero* to oxcarbazepine alone, 26 cases of malformations were described. By estimating the proportion of each subgroup of malformations compared to the total number of malformations, the proportions of dysplasia of the hip (4/26; 15%) and oral clefts (3/26; 12%) appear higher than the proportions expected according to EUROCAT. Nevertheless, in the light of the small number of cases, the lack of detail on the risk factors, other than concomitant antiepileptic exposure (such as the mother's history, alcohol consumption, exposure to other drugs or substances, etc.) and the different methodologies used in the studies (definitions of malformations, prospective and retrospective data collection, child follow-up time, etc.), these data must be considered with caution and cannot be used to make a comparison with the general population, or to conclude as to the malformative profile of oxcarbazepine. Moreover, study conducted in 2017 by ANSM and CNAM report that a risk of 26 major congenital malformations studied did not differ between the children born to mothers exposed to oxcarbazépine in monotherapy (N = 140) and children born to mothers not exposed during pregnancy.

Clinical data - Dose-effect relationship

No studies on the dose-effect relationship have been identified for oxcarbazepine.

Conclusion on the malformation risk

Therefore, in the current state of knowledge, moderate data from follow-up of pregnancies exposed to oxcarbazepine monotherapy (300 - 1000 pregnancies) do not agree with a considerable increase in the overall risk of malformations. Further studies are required to confirm or disprove it. Nevertheless, the malformation risk must continue to be monitored on the whole, and for different types of malformations.

NEURODEVELOPMENTAL RISK

In a study conducted in 2018 by ANSM and CNAM, exposure to oxcarbazépine appears to be associated with a risk of having a consultation with an orthoptist which increased by almost 2 times (31 cases among 143 children exposed; HR = 1.7 (1.2-2.4)), but this association is one-off and does not persist when the analysis is restricted to a children born to mothers without an identified psychiatric illness.

a) DQ and IQ scores

In the current state of knowledge, no conclusive data on the subject of neurodevelopmental risk.

b) Autism spectrum disorder

The most robust study from a methodological standpoint in terms of number of children, acknowledgement of relevant confounding factors and clinical diagnosis, although retrospective, does not report a statistically-significant difference in the risk of PDD and infantile autism in the 321 children born to mothers treated with oxcarbazepine, with immediate risks of 2.1 (0.96 - 4.6) and 1.0 (0.1 - 6.9) respectively (Christensen *et al.*, 2013). Nevertheless, the data are too few to be able to come to a final conclusion and additional epidemiological studies are necessary to confirm or invalidate the results.

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PERAMPANEL

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective (especially progestin). Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Data in animals

Animal data are rather reassuring showing absence of malformative toxicity but poorly defined pre- and post-natal toxicity, appears to exist.

Clinical data

There are very few data on the use of perampanel during pregnancy. The few clinical observations in monotherapy are almost non-existent and do not make it possible to conclude. The data for polytherapy are inconsistent.

NEURODEVELOPMENTAL RISK

To date, the data relating to the neurodevelopmental risk further to exposure *in utero* to perampanel alone are non-existent or almost non-existent, not enabling a conclusion.
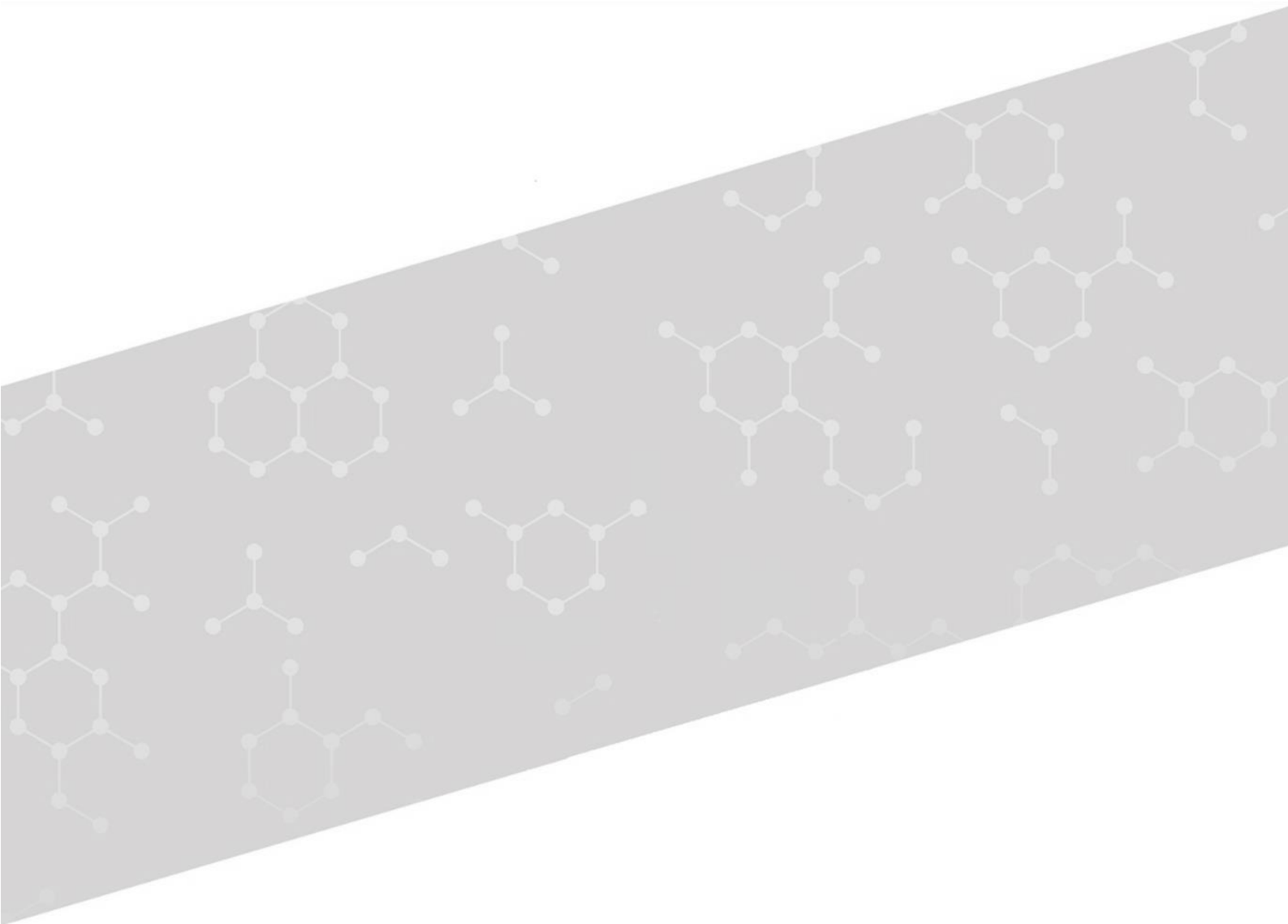
PHENOBARBITAL / PRIMIDONE

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Data in animals

In animals, the experiments carried out on a single species (mice) show a teratogenic effect of the cleft palate type

Clinical data – Overall frequency of malformations

Data available on the malformation risk from phenobarbital cover relatively small numbers with respect to the age of the substance and with respect to the other antiepileptics. The data are even fewer for primidone. Therefore, the data used for phenobarbital shall apply to primidone.

The 2 larger prospective studies in terms of the number of exposed pregnancies, namely Tomson *et al*., 2018 (n = 294) and Hernandez-Diaz *et al*., 2012 (n = 199) report a statistically-significant increase in malformation after exposure *in utero* to phenobarbital, by comparison with the non-epileptic control group (RR = 5.1 (1.8 – 14.9)) or treated with lamotrigine (RR = 2.9 (1.4 – 5.8) (Hernandez-Diaz *et al*., 2012) or 2.3 (1.4 – 3.8) (Tomson *et al*., 2018)). It should be noted that in the study by Hernandez-Diaz *et al*., 2012, the risk is no longer statistically-significant when only the purely prospective cases are examined (RR = 2.5 (0.9 - 6.8)), as the estimated risk is roughly the same, it cannot be ruled out that the loss of significance is related to a loss of statistical power. In the same way, this increased risk is not found or does not reach statistical significance in the other cohort or register studies or the case-control study. Nevertheless, it should be noted that the numbers in these studies are lower than those in the studies by Hernandez-Diaz *et al*., 2012 and Tomson *et al*., 2018. In effect, in their meta-analyses Weston *et al*., 2016 report that the children exposed *in utero* to phenobarbital have a mean pooled rate of malformations of 7.10% (5.36% – 9.08%) (n = 709), statistically higher than that of the non-epileptic control groups (RR = 2.84 (1.57 – 5.13); n = 345 *versus* 1591) and than that of children exposed *in utero* to levetiracetam, gabapentin or lamotrigine, but not reaching statistical significance compared to the untreated epileptics group (RR = 1.95 (0.97 - 3.93)).

Conclusion on the overall frequency of malformations

Therefore, data currently available agree with an increase in the overall frequency of malformations related to exposure *in utero* to phenobarbital, around 3 times higher than the frequency observed in the general population. If, after re-assessment, treatment is required, this risk is to be considered in the choice of treatment and should be taken into account in the event of exposure during the pregnancy.

Clinical data – Type of malformations

In the current state of knowledge, exposure *in utero* to phenobarbital leads to an increased risk of cardiac malformations, cleft lip and/or palate and hypospadias. Other types of malformations, especially craniofacial (microcephalia, facial dysmorphia, etc.) and finger (hypoplasia of the phalanges and nails etc.) were also reported (Battino *et al*., 1992; Jones *et al*., 1992; Arpino *et al*., 2000; Holmes *et al*., 2001; Tomson *et al*., 2018; Tomson et Battino, 2012; Hernandez-Diaz *et al*., 2012; Tomson *et al*., 2016; CNAM/ANSM 2017).

Clinical data - Dose-effect relationship

To date, a dose-effect relationship was shown for phenobarbital in one study (Tomson *et al*., 2018), in particular from 130 mg/day, but is not found in another study of equivalent size (Hernandez-Diaz *et al*., 2012). Further studies are required to confirm or disprove the dose-dependence.

NEURODEVELOPMENTAL RISK

Generally, the studies available concerning the DQ and IQ of children exposed *in utero* to phenobarbital are contradictory, cover small numbers, and most do not take the relevant maternal parameters into account, or cover exposure at the end of pregnancy. The most recent studies, taking the potential confounding factors into account did not evaluate phenobarbital.

Preschool children

Concerning development quotients, the 2 studies available do not show a significant difference in DQ among the children exposed *in utero* to phenobarbital (n 35 and 41 respectively) compared to the children born to phenytoin-treated or untreated mothers (Shapiro *et al*., 1976) or compared to the children born to untreated non-epileptic or carbamazepine-, valproate- or phenytoin-treated mothers (Thomas *et al*., 2008). This study also reports an increased risk of motor QD delay (score < 84) compared to the children exposed to the other antiepileptics examined (valproate, carbamazepine and phenytoin), which is not found for the mental DQ. Nevertheless, the results of these studies are to be considered with caution, given their limits, especially in terms of absence of acknowledgement of the maternal parameters (the study by Shapiro *et al*., 1976 adjusting on the socio-economic status). In clinical trials with administration of phenobarbital at the end of

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pregnancy, no statistically-significant reduction is reported in the study of children age 18-22 months (n = 226) (Shankaran *et al.*, 2002), but a reduction in mental DQ is reported in smaller studies in children age 2 (n = 59) (Thorp *et al.*, 1999) and 3 (n = 41) (Shankaran *et al.*, 1996).

School-age children

Concerning intellectual quotients, Thomas *et al.*, 2007 and Titze *et al.*, 2008, report a reduction in IQ among the children exposed *in utero* to phenobarbital compared to the children born to non-epileptic mothers. Nevertheless, each study only includes 14 children, and the first does not take the relevant maternal parameters into account, and the second does not differentiate exposure to phenobarbital alone or combined. It should be noted that a reduction in IQ is also reported for the 15 children exposed to primidone alone or in combination (Titze *et al.*, 2008). This risk is not found in the study by Shapiro *et al.*, 1976 (adjusting on the socio-economic status, but not on the other relevant maternal parameters) by evaluating the role of exposure to phenobarbital among children of non-epileptic mothers; nor for primidone in the study by Koch *et al.*, 1999, however, this study only covers 9 children. By comparison with the children exposed to the other monotherapies, the study based on the Indian register finds an increased risk at the limit of statistical significance, at the age of 6 years (n = 14) and statistical risk at the age of 10-12 years (n = 22) (Thomas *et al.*, 2007 and Gopinath *et al.*, 2015). This increased risk compared to the other treatments, is not found in the study by Holmes *et al.*, 2005 (n = 17), however the control group in this study includes exposure to phenobarbital, which means the results cannot be interpreted. Learning disorders (spelling and arithmetic) were reported in a very small study (n = 7-12) not taking maternal parameters into account (Van Der Pol *et al.*, 1991). The most methodologically robust study, although retrospective, covers a small number, but reports a statistically-significant reduction in overall IQ (of around 7 points) in 33 men (average age 23) exposed *in utero* to phenobarbital compared

to the untreated control group (n = 52), matched on socio-economic status, the mother's and father's age, single-parent family status, unplanned pregnancy, 1st child, level of education of the head of the family, a predisposition risk score, pregnancy duration, birth weight and size, smoking in the last trimester and maternal weight gain (Reinisch *et al.*, 1995). It should be noted that the data on behavioural disorders cover too small numbers to be able to come to a conclusion (Van Der Pol *et al.*, 1991 and Dean *et al.*, 2002).

Moreover, in the 2018 study conducted by ANSM and CNAM, the risk of "behavioral and emotional disorders that usually appear during childhood and adolescence" is higher among children born to mothers without an identified psychiatric illness exposed to phenobarbital compared to children not exposed. Furthermore, this result should be considered with caution because it is based on only one single case among exposed children.

Conclusion on the neurodevelopmental risk

Data available are divergent, cover small numbers and contain significant methodological bias, making it difficult to interpret the results and not making it possible to come to a final conclusion. As the most methodologically-robust study reports a reduction in IQ in adulthood among 33 children exposed *in utero* to phenobarbital, the risk cannot be ruled out. If, after re-assessment, treatment is required, this risk is therefore to be considered in the choice of treatment and should be taken into account for follow-up of the child in the event of exposure during the pregnancy. Nevertheless further studies are required to confirm or disprove the risk.

PHENYTOIN / FOSPHENYTOIN

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Data in animals

Phenytoin is teratogenic in rats and mice: the most common malformations are cranio-facial, with especially cleft palate and pre and postnatal growth retardation. An equivalent toxicological profile was shown for fosphenytoin (phenytoin prodrug).

Clinical data – Overall frequency of malformations

Data available on the malformation risk from phenytoin cover relatively small numbers with respect to the age of the substance and with respect to the other antiepileptics.

Larger studies in terms of number of exposed pregnancies, namely the 4 prospective studies, Kaneko *et al*., 1999 (n = 132), Kaaja *et al*., 2003 (n = 124), Tomson *et al*., 2018 (n = 125) and Hernandez-Diaz *et al*., 2012 (n = 416) and the study conducted by cross-referencing Swedish registers (Kallen *et al*., 2013; n = 140) report high malformation rates after exposure *in utero* to phenytoin between 2.4% and 9.1%. This variability may be related to the different methodologies between the studies, to the doses administered, etc. According to the meta-analyses conducted by Weston *et al*., 2016, the children exposed *in utero* to phenytoin have a mean malformation rate of 6.26% (4.37% – 8.47%; n = 1,279; 25 studies). As the overall frequency of malformations in the general population is 2-3%, exposure *in utero* to phenytoin leads, according to the studies, to an overall frequency of malformations either similar to the general population, or 2 to 3 times higher than it.

In the same studies, a non-statistically-significant increase in malformation after exposure *in utero* to phenytoin is reported by comparison with control groups of untreated epileptic women (OR = 3.2 (p > 0.05) in Kaneko *et al*., 1999; ORa = 1.7 (0.6 – 4.6) by considering the mono- and polytherapies in Kaaja *et al*., 2003). In the same way, by comparison with control groups of untreated, non-epileptic women or the general population, Hernandez-Diaz *et al*., 2012 and Kallen *et al*., 2013 report a non-statistically significant increase in malformation after exposure *in utero* to phenytoin (RR = 2.6 (0.9 – 7.4) and ORa = 1.84 (0.95 - 3.21)). A non-statistically-significant increase in the overall frequency of malformations among children born to mothers treated with phenytoin is also observed compared to children born to mothers treated with lamotrigine (RR = 1.5 (0.7 – 2.9) (Hernandez-Diaz *et al*., 2012); while this difference is statistically-significant in Tomson *et al*., 2018 (OR = 2.3 (1.1 – 4.8), is not calculated by the authors). Therefore, these studies

all agree with an increase in the overall frequency of malformations, of course, non-statistically-significant but which is probably related to a lack of power, which seems to be shown by the meta-analysis by Weston *et al*., 2016, which confirms a malformation risk from phenytoin monotherapy. In effect, in their meta-analyses Weston *et al*., 2016 report that the children exposed *in utero* to phenytoin have a mean rate of malformations of 6.26% (95% CI: 4.37% – 8.47%) (n = 1,279), statistically higher than that of the unexposed children born to mothers without epilepsy (RR = 2.38 (1.12 - 5.03)), of the children born to untreated epileptic mothers (RR = 2.40 (1.42 - 4.08)), of the children born to lamotrigine- (RR = 1.89 (1.19 - 2.94)) or levetiracetam-treated (RR = 2.04 (1.09 - 3.85)) epileptic mothers. In contrast, compared to the children born to mothers treated with valproate, the risk appears to be two times lower (RR = 2.00 (1.48 - 2.71)).

Therefore, data currently available agree with an increase in the overall frequency of malformations related to exposure *in utero* to phenytoin, around 2 to 3 times higher than the frequency observed in the general population. If, after re-assessment, treatment is required, this risk is to be considered in the choice of treatment and should be taken into account in the event of exposure during the pregnancy.

Clinical data – Type of malformations

In the current state of knowledge, exposure *in utero* to phenytoin leads to an increased risk of cardiac malformations, cleft lip and/or palate and hypospadias. Other types of malformations, especially craniofacial (hypertelorism, facial dysmorphia etc.), microcephalia and of the fingers (hypoplasia, absence of distal phalanx etc.) were also reported (Kelly *et al*., 1984; Gaily 1990; D'Souza *et al*., 1990; Gladstone *et al*., 1992; Nulman *et al*., 1997; Gaily *et al*., 1988; Holmes *et al*., 2001; Dean *et al*., 2002; Morrow *et al*., 2006; Puho *et al*., 2007; Hernandez-Diaz *et al*., 2012).

Clinical data - Dose-effect relationship

To date, a dose-effect relationship was mentioned in one study, but not found in the other studies looking at the dose-effect relationship between the phenytoin dose and the malformation risk. Nevertheless, in the light of the small numbers in these studies, additional studies are necessary to conclude on the dose- dependence.

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NEURODEVELOPMENTAL RISK

Generally, it would appear that the studies available concerning neurodevelopmental disorders among children exposed *in utero* to phenytoin cover small numbers.

Preschool children

Concerning development quotients, among the studies available, 3 do not show a significant difference in DQ among the children exposed *in utero* to phenytoin (n 40, 21 and 29 respectively) compared to the children born to phenobarbital-treated or untreated mothers (Shapiro *et al*., 1976) or compared to the children born to untreated non-epileptic or carbamazepine-treated mothers (Wide *et al*., 2000) or compared to children born to untreated epileptic mothers (Thomas *et al*., 2008). The results of these studies are to be considered with caution given their limits, especially the small number of exposed pregnancies and the fact that maternal parameters are not taken into account (especially for the studies by Wide *et al*., 2000 and Thomas *et al*., 2008; the study by Shapiro *et al*., 1976 adjusting on socio-economic status). Among the data available, 2 studies take account of the relevant maternal parameters (i.e. Socio-economic status, IQ, mother's, parity and gravidity, etc.) (Scolnick *et al*., 1994 and Meador *et al*., 2009). Scolnick *et al*., 1994 report a lower overall DQ/IQ, scores lower in the verbal tests and an increased frequency in delay (DQ/IQ < 84) among the children exposed *in utero* to phenytoin (n = 34) compared to the group of children born to non-epileptic mothers. Meador *et al*., 2009 do not observe a difference in overall DQ among the children exposed *in utero* to phenytoin (n = 48) compared to those exposed to lamotrigine or carbamazepine; whereas the DQ is significantly higher among these children than those exposed *in utero* to valproate (99 *versus* 92; p = 0.04). It should be noted that the study by Bromley *et al*., 2010, adjusting on the relevant risk factors, reports a statistically-significant decrease in DQ (p = 0.033), and an increased risk of delay among pre-school children (DQ < 84; p = 0.007) in the "other monotherapy" group (n = 13 of which 7 children exposed *in utero* to phenytoin) compared to the non-epileptic control group, but without individual details on the antiepileptics examined. By comparing antiepileptics, the meta-analysis by Bromley *et al*., 2014 reports that among young children, there was no significant difference between the DQ of the children exposed to carbamazepine (n = 172) and that of the children exposed to phenytoin (n = 87) (MD 3.02, CI 95% of -2.41 to 8.46, p = 0.28). The DQ of the children exposed to phenytoin (n = 80) was higher than among those exposed to valproate (n = 108) (MD 7.04, CI 95% from 0.44 to 13.65, p = 0.04).

School-age children

During longitudinal follow-up, Wide *et al*., 2002 do not report a significant difference in the overall IQ score, but observe a significant difference in locomotor score among the children exposed *in utero* to phenytoin (n = 15; 98 *versus* 106). Among children age 4, Shapiro *et al*., 1976 (adjusting on socio-economic status, but not on the other relevant maternal

parameters) do not see a difference in overall IQ of the children exposed *in utero* to phenytoin (n = 35) compared to the children born to mothers treated with phenobarbital or untreated. The retrospective study conducted by Adab *et al*., 2004 does not report a statistically-significant difference in IQ among children between the age of 6 and 16 born to mothers treated with phenytoin (n = 21) compared to unexposed children (n = 80). In the same way, the study based on the Indian register, does not report a statistically-significant difference in IQ among the children exposed *in utero* to phenytoin compared to the children born to non-epileptic mothers (at the age of 6 and 10-12 years respectively; Thomas *et al*., 2007 and Gopinath *et al*., 2015). Nevertheless, this study only includes 5 children age 6 years and 11 age 10-12 years and does not take the relevant maternal parameters into account. In contrast, Titze *et al*., 2008 report a reduction in IQ among the children exposed *in utero* to phenytoin (n = 24) compared to the children born to non-epileptic mothers. Nevertheless, this study does not differentiate exposure to phenytoin alone or in combination for the second. The study with the most robust methodology, taking relevant confounding factors into account (mother's age, mother's IQ, standard dose, gestational age at the birth, pre-conception folic acid supplementation) reports that prenatal exposure to phenytoin (n = 43 and n = 40 at 4.5 and 6 years respectively) does not lead to a statistically-significant difference in overall IQ compared to the children exposed *in utero* to lamotrigine or carbamazepine. In contrast, the children exposed *in utero* to phenytoin have a statistically higher overall IQ (of around 10 points) than that of children exposed *in utero* to valproate (p = 0.0156 at 4.5 years and p = 0.0004 at 6 years) (Meador *et al*., 2011 and 2013). By comparing antiepileptics, the meta-analysis by Bromley *et al*., 2014 reports that among school-age children, the intellectual quotient (IQ) of the children exposed to carbamazepine (n = 150) was not different from that of the children exposed to phenytoin (n = 45) (MD -3.30, CI 95% of -7.91 to 1.30, p = 0.16). The IQ of the children exposed to phenytoin (n = 45) was higher than among those exposed to valproate (n = 61) (MD 9.25, CI 95% from 4.78 to 13.72, p < 0.0001).

Developmental delay was studied by Dean *et al*., 2002 who evaluated development (speech and/or motricity) of children exposed *in utero* to phenytoin. The analysis showed that phenytoin monotherapy was closely related to developmental delay (especially motor). This difference remained significant when children with a family history of neurodevelopmental disorders were removed from the analysis (mother's IQ not taken into account however).

Conclusion on the neurodevelopmental risk

In the current state of knowledge, evaluation of neurodevelopmental disorders related to exposure *in utero* to phenytoin remains uncertain. In effect, data available are divergent, cover small numbers and some contain methodological bias, making it difficult to interpret the results. Among the studies taking relevant potential confounding factors into account, the most recent data does not necessarily

find a relationship (in terms of impact on the IQ), but older studies report an increased risk. Also, the experimental data show an impact form the treatment and indirectly make the hypothesis of a relationship plausible. In the light of the data available, the risk cannot therefore be ruled out; if a relationship exists, the current data cannot characterise it. Therefore, further studies are required to confirm or disprove the risk.

If, after re-assessment, treatment is required, this risk is to be considered in the choice of treatment and should be taken into account for follow-up of the child in the event of exposure during the pregnancy.

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PREGABALIN

INTERACTIONS WITH HORMONAL CONTRACEPTION

Concomitant administration of pregabalin and oral contraceptives such as norethindrone and/or ethinylestradiol does not modify the pharmacokinetic parameters in steady state of either of the substances.

MALFORMATION RISK

Data in animals

Pregabalin is not teratogenic in mice. In rats and rabbits, skeletal defects were reported at high maternal doses.

Clinical data

Data currently available covering the risk of malformation after exposure *in utero* to pregabalin are limited (< 200 women followed-up prospectively). Nevertheless, the largest study published to date on the consequences of exposure *in utero* to pregabalin report a statistically-significant increased risk of malformations among the children exposed *in utero* to pregabalin compared to unexposed children (Winterfeld *et al*., 2016). In effect, the rate of major congenital malformations is significantly higher in children exposed *in utero* to pregabalin in the 1st trimester of pregnancy and after ruling out chromosome anomalies; with 7 cases of malformations out of 116 children exposed (6%) *versus* 12 out of 580 controls (2.1%), i.e. OR = 3 (1.2 - 7.9). The authors report an increased risk of central nervous system malformations. In the light of the limits of the study (relatively small sample size, co-exposure to other drugs and differences between the groups), it is not possible to draw final conclusions and larger independent studies are necessary to confirm/invalidate these results. These results were not retrieved in a retrospective study on 2 American databases including 353 and 116 pregnancies exposed at a pregabalin monotherapy during the 1st trimester, respectively. Compelling the 2 results from each database, RRa was equals to 1.02 (0.69 – 1.51) (Patorno *et al*., 2017).

Moreover, a study conducted in 2017 by ANSM and CNAM identifies a potential risk in children born to mothers exposed to pregabalin during pregnancy (cardiopathy and craniostenosis) compared to children born to unexposed mothers.

Conclusion on the malformation risk

These results are potential signals of a risk of major malformations (especially a statistically-significant increase in central nervous system malformations) after exposure to pregabalin in the first trimester of pregnancy, and are therefore to be taken into consideration. Therefore, monitoring of the malformation risk must be continued on the whole and in particular for the types of malformations for which a potential signal has been identified, with additional research.

NEURODEVELOPMENTAL RISK

To date, data from scientific literature relating to the neurodevelopmental risk further to exposure *in utero* to pregabalin alone are non-existent or almost non-existent, not enabling a conclusion. Furthermore, in a study conducted in 2018 by ANSM and CNAM, exposure to pregabalin appears to be associated with a global risk of diagnosis of mental and behavior disorders increased by 1.5 (HR = 1.5 (1-2.1)), with in particular an increased risk of "mental retardation" (not statistically significant: number of cases exposed = 7; HR = 1.7 (0.8-3.6)) and of having a consultation with an orthoptist (HR = 1.2 (1.1-1.4)). Considering only children born to mothers without an identified psychiatric illness, there is a high association with the risk of mental retardation (HR=3.1 (1.2-8.3)) and an association with the risk of having a consultation with an orthoptist persist (HR = 1.4 (1.1 – 1.6)). An increased risk of mental retardation among children exposed to pregabalin as well as an increased risk of having a consultation with an orthoptist constitute a signal which require additional research

RETIGABINE

INTERACTIONS WITH HORMONAL CONTRACEPTION

For retigabine doses up to 750 mg per day, retigabine did not have a clinically-significant effect on the pharmacokinetics of the oestrogen compounds (ethinylestradiol) and progestin compounds (norethisterone) of oral contraceptive pills. Also, there was no clinically-significant effect from low-dose contraceptive pills on the pharmacokinetics of retigabine.

MALFORMATION RISK

Data in animals

No effect on fertility is reported. No teratogenic effect was observed, but changes in soft tissue in the presence of maternal toxicity, at exposure lower than the maximum human doses was. An increase in mortality and impaired sound stimulus response were found in one species at a low dose, but in the presence of maternal toxicity. In conclusion, the dose levels tested in the animal were lower than the therapeutic doses used in humans, due to the maternal toxicity from low doses. Animal studies on reproductive toxicity are therefore insufficient to be able to come to a conclusion.

Clinical data

To date, data in humans count 8 prospective cases of maternal exposure during the 1st trimester without suggestion of a malformation risk. The 3 assessable retrospective cases (abortions, excluded) of maternal exposure during the 1st trimester include 2 births without malformation and one child with polydactyly (for which the relationship with valproate can be suggested), persistent ductus arteriosus, retinopathy and inguinal hernia (in which prematurity is likely to play a role). Given the absence of cases with exposure after the 1st trimester, the foetal and neonatal risk cannot be evaluated. In conclusion, data in humans is to date insufficient to evaluate the malformation, foetotoxic and neonatal risk from retigabine.

NEURODEVELOPMENTAL RISK

A single case from the EURAP (International Registry of antiepileptic Drugs and Pregnancy) register, mentions normal follow-up after 1 year of a child exposed *in utero* to retigabine (in combination) in the 1st trimester of pregnancy. To date, the clinical data relating to the neurodevelopmental risk further to exposure *in utero* to retigabine alone are non-existent or almost non-existent, not enabling a conclusion.

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RUFINAMIDE

INTERACTIONS WITH HORMONAL CONTRACEPTION

The interaction with hormonal contraceptives is to be taken into consideration since the treatment can render hormonal treatment ineffective, by increasing its hepatic metabolism. Another effective contraception method should be recommended/prescribed.

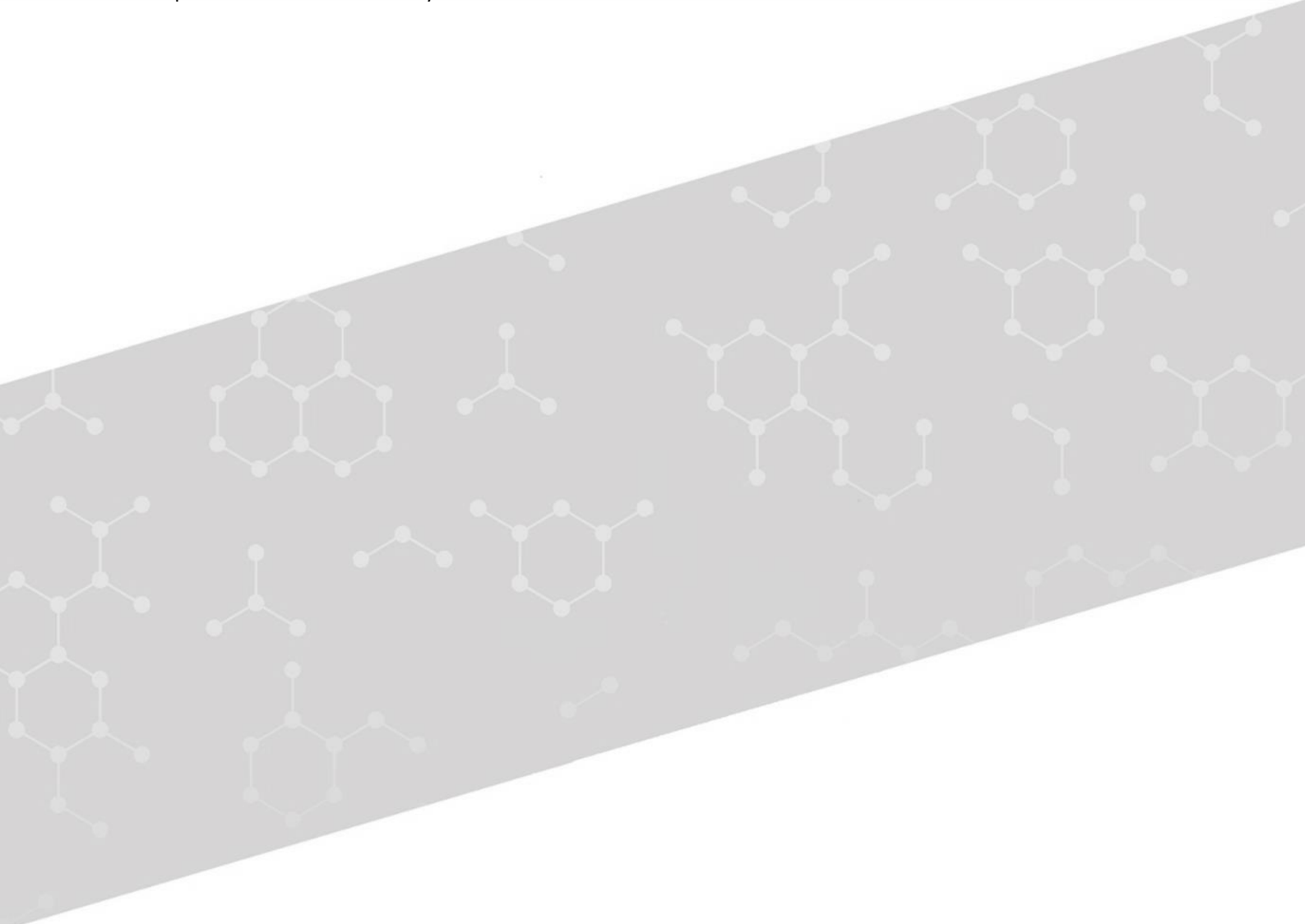## MALFORMATION RISK

Data in animals

No effect on fertility has been demonstrated. Skeletal malformations are found in two species and visceral defects in one of the two species tested, at low doses but having led to maternal toxicity. Foetal death and low foetal weight were observed, also at low doses but having led to maternal toxicity. No postnatal effect was observed at high doses in one species, but an increase in stillbirth rate is seen in another species at maternotoxic doses. No genotoxic effect was identified. In conclusion, the animal studies show, either absence of teratogenic or foetotoxic effect, or a teratogenic or foetotoxic effect in the presence of maternal toxicity.

Clinical data

To date, no data is available concerning the risks related to exposure *in utero* to rufinamide alone. Around ten pregnancy outcomes were collected after exposure *in utero* to rufinamide in combination, without any malformation being identified among the live births (foetal malformation status not given for the abortions). Therefore, data available in humans is insufficient to evaluate the malformation, foetotoxic and neonatal risk from rufinamide.

NEURODEVELOPMENTAL RISK

To date, the clinical data relating to the neurodevelopmental risk further to exposure *in utero* to rufinamide alone are non-existent or almost non-existent, not enabling a conclusion.

TIAGABINE

INTERACTIONS WITH HORMONAL CONTRACEPTION

Tiagabine did not show clinically-significant effects on the plasma oral contraceptive hormone concentrations.

MALFORMATION RISK

Data in animals

No effect on fertility has been demonstrated. Various malformations were observed in rats in the presence of maternal toxicity, but no malformation was seen in rabbits. Embryo loss and foetal variations were observed in rabbits in the presence of maternal toxicity. An increase in foetal loss was observed in rats at low doses and a reduction in foetal weight at maternotoxic doses. In conclusion, the animal studies show a teratogenic or foetotoxic effect at high doses in the presence of maternal toxicity, except for the increase in foetal death after administration of low doses at the end of gestation in one species.

Clinical data

Data on human exposure to tiagabine at least in the 1st trimester of pregnancy with known outcome count to date (Morrel *et al.*, 1996; Leppik *et al.*, 1999; Neppe *et al.*, 2000; Vajda *et al.*, 2014; spontaneous reports):

♦ 15 pregnancies in monotherapy followed-up prospectively, with 5 normal births, 3 miscarriages (i.e. Rate of 20%), 1 ectopic pregnancy (6%), 6 abortions.

♦ 9 pregnancies in monotherapy followed-up retrospectively with 6 normal births, 1 miscarriage, 2 abortions.

♦ 15 pregnancies in polytherapy followed-up prospectively, with 9 normal births, 1 miscarriage (6.6 %), 1 ectopic pregnancy (6.6 %), 4 abortions.

♦ 20 pregnancies in polytherapy followed-up retrospectively with 9 normal births, 1 birth with malformation, 6 miscarriages, 1 ectopic pregnancy, 1 foetal death *in utero*, 2 abortions.

The only two cases of malformations after exposure *in utero* to tiagabine are retrospective cases from the pharmaceutical company, of which one exposure time to tiagabine is not specified and with co-exposure to valproate, which does not indicate target organs.

In the absence of clinical information on the pharmaceutical company's case with exposure throughout the pregnancy (1 prospective case and 3 retrospective cases in monotherapy), we have no data on the foetal or neonatal risk from tiagabine.

In conclusion, data in humans is to date insufficient to evaluate the malformation, foetotoxic and neonatal risk from tiagabine.

NEURODEVELOPMENTAL RISK

To date, the clinical data relating to the neurodevelopmental risk further to exposure *in utero* to tiagabine alone are non-existent or almost non-existent, not enabling a conclusion.

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TOPIRAMATE

INTERACTIONS WITH HORMONAL CONTRACEPTION

Interaction with hormonal contraceptives is to be taken into consideration since the treatment can render contraception ineffective, especially topiramate doses of ≥ 200 mg/day can lead to failure of hormonal contraceptives containing ethinylestradiol. Another effective contraception method should be recommended/prescribed.

MALFORMATION RISK

Data in animals

Topiramate showed a teratogenic effect in the species studied (mice, rats and rabbits). A reduction in foetal weight and/or late skeletal ossification were observed in mice and rats. Topiramate caused cranio-facial malformations in mice and skeletal malformations (finger and limb defects, vertebral and rib malformations) in rats and rabbits.

Clinical data – Overall frequency of malformations

According to the study, and while considering (for the registers) the latest data published, the overall frequency of occurrence of major malformations among children exposed *in utero* to topiramate monotherapy at least in the first trimester varies between 1.96% and 8.2% (Morrow *et al.*, 2006; Ornoy *et al.*, 2008; Tomson *et al.*, 2018; Hernandez-Diaz *et al.*, 2012; Green *et al.*, 2012; Margulis *et al.*, 2012; Kallen *et al.*, 2013; Veiby *et al.*, 2014; and Vajda *et al.*, 2016). This variability can of course be explained partly by the different study methodologies, the treatment durations and doses administered, etc., but if we compare the overall frequency of malformations in the general population (2-3%), exposure *in utero* to topiramate seems nevertheless to lead, depending on the study, to a higher mean overall frequency of malformations than in the general population. In addition, considering, among the 5 prospective studies published, the prospective study with the largest number of pregnancies exposed to topiramate (NAAED register; Hernandez-Diaz *et al.*, 2012 ; n = 359), a statistically-significant increase in malformations after exposure *in utero* to topiramate monotherapy is observed, compared to a control group:

♦ external (RR = 2.0 (1.2 – 3.3)) (after exclusion of the malformations diagnosed after the age of 5 days to be comparable);

♦ internal unexposed (RR = 3.8 (1.4 – 10.6))

♦ internal treated with lamotrigine (RR = 2.5 (1.2 - 5.2), only taking the purely prospective cases into account)

The other studies available making the comparison with internal control groups of other studies (either unexposed, or exposed to another antiepileptic), also agree with an increased, not necessarily significant malformation risk, but the numbers are a lot smaller (fewer than 50 pregnancies per series) and the methodologies are not as strict except for the UKEPR (UK and Ireland epilepsy and Pregnancy registers; Morrow *et al.*, 2006 ; n = 28 pregnancies) and EURAP (International Registry of antiepileptic Drugs and Pregnancy (Tomson *et al.*, 2018) ; n = 152 pregnancies). A study conducted in 2017 by ANSM and CNAM reports that children exposed *in utero* to topiramate have an increased overall risk of major malformations (all 26 major congenital malformations studied) of the order of 2 to 3 times higher than children unexposed *in utero* (OR = 2.3 (1.3-4.1)).

The increased risk is confirmed by the meta-analyses by Weston *et al.*, 2016, who observe that the children exposed *in utero* to topiramate have a mean rate of malformations of 4.28 % (2.65 % – 6.29%) (n = 473; 3 studies), statistically higher than that of the non-epileptic control groups (RR = 3.69 (1.36 – 10.07); n = 359 *versus* 442) and than that of children exposed *in utero* to levetiracetam or lamotrigine, but not reaching statistical significance compared to the untreated epileptics group.

Clinical data – Type of malformations

♦ An increased risk of oral clefts (cleft lip +/- palate) after exposure *in utero* to topiramate is reported in several studies which agree (Hunt *et al.*, 2008; Hernandez-Diaz *et al.*, 2010; Margulis *et al.*, 2012; Castilla-Puentes *et al.*, 2014; Mines *et al.*, 2014; Alsaad *et al.*, 2015; Hernandez-Diaz *et al.*, 2018 ; ANSM/CNAM 2017). This risk appears to be difficult to quantify precisely. In the light of the available data, this risk could be 2 to 10 times higher among the children exposed *in utero* to topiramate in the 1st trimester of pregnancy than in the general population. It should be noted that this risk is around 0.1 - 0.2% in the general population.

♦ An increased risk of hypospadias is mentioned in 2 of the 3 prospective studies (Hunt *et al.*, 2008; Hernandez-Diaz *et al.*, 2012) and in two retrospective studies examining exposure to topiramate monotherapy, during the 1st trimester of pregnancy (Kallen *et al.*, 2013; Castilla-Puentes *et al.*, 2014). Nevertheless, it should be noted that no statistical analysis is provided concerning the specific risk of hypospadias.

♦ Relationships between exposure *in utero* to topiramate and other types malformations have also been reported, but in studies including exposure in mono- and polytherapy (Vajda *et al.*, 2013 et Tennis *et al.*, 2015), which does not make it possible to conclude on the role of topiramate.

Clinical data - Dose-effect relationship

Data currently available agrees with a dose-effect relationship, but this remains to be confirmed, and the data available cannot be used to determine a threshold dose (Hunt *et al.*, 2008 and Vajda *et al.*, 2016).

Conclusion on the malformation risk

Therefore, in the current state of knowledge, the data show an increase in the overall frequency of malformations related to exposure *in utero* to topiramate, to be taken into consideration (especially in terms of prescription and information) and potentially supported by a specific malformation (oral clefts and hypospadias). If, after re-assessment, treatment is required, this risk is to be considered in the choice of treatment and should be taken into account in the event of exposure during the pregnancy.

ANTHROPOMETRIC PARAMETERS

Growth retardation is reported in studies looking at these parameters (Ornoy *et al.*, 2008; Hernandez-Diaz *et al.*, 2014; Veiby *et al.*, 2014; Kilic *et al.*, 2014). Among the children born to mothers treated with topiramate, a low birth weight (between 161 and 368 g according to the studies), and an increased risk of small for gestational age (SGA) are observed (with, according to the studies: RR = 3.5 (2.1 – 5.7); ORa = 3.29 (1.70 – 6.39); RR = 1.8 (1.0 – 3.1)) along with an increased risk of microcephalia (ORa = 7.21 (3.23 - 16.1)). An effect on weight from topiramate is also pharmacologically plausible. In effect, weight loss or absence of weight gain among growing children was observed in clinical studies with topiramate, justifying close monitoring of the mother's weight (from the start of the pregnancy) and nutritional supplementation or increased calorie intake if necessary.

NEURODEVELOPMENTAL RISK

To date, the clinical data on the neurodevelopmental impact of prenatal exposure to topiramate are limited.

According to study conducted in 2018 by ANSM and CNAM, exposure to topiramate appears to be associated with an almost 1.4 times higher risk of having a consultation with an orthoptist, but this association is one-off and does not persist when the analysis is restricted to children born to mothers without an identified psychiatric illness. A study based on a limited number of pregnancies (n = 27) does not indicate an higher risk in children exposed *in utero* to topiramate compared to non exposed children (n = 55), in terms of IQ and behavioural parameters assessed at 6 years old (Bromley *et al.*, 2016). Nevertheless, the study by Rihtman *et al.*, 2012 conducted in 9 children (from 3 to 7 years) exposed *in utero* to topiramate, shows in particular, an increased risk of visual and spatial and motor control difficulties and learning difficulties in a high proportion of children (5/9; 56%). This study, despite its methodological weaknesses (small number of children exposed, absence of acknowledgement of potential confounding factors, non-blinded evaluation, etc.) and the cases of spontaneous reports and the few experimental data on the potential neurotoxicity of topiramate are a strong signal which must be taken into consideration in the choice of treatment, and must be taken into account for follow-up of the child in the event of exposure during pregnancy.

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VIGABATRIN

INTERACTIONS WITH HORMONAL CONTRACEPTION

Data relating to the interactions with hormonal contraceptives are missing.

MALFORMATION RISK

Data in animals

Animal studies showed teratogenicity from vigabatrin in rabbits, with an increase in the incidence of cleft palate at the 2 highest doses tested.

Overall frequency of malformations

Data currently available on exposure to vigabatrin during pregnancy are very limited, with 12 pregnancies exposed in monotherapy at least during the 1st trimester and collected prospectively, among which no major malformations are reported (Morrow *et al.*, 2006; Tomson *et al.*, 2011; Vajda *et al.*, 2014). Cases of malformations (4 after exposure at least in the 1st trimester of pregnancy and 3 for which exposure time is not known) were reported among the pregnancies exposed to vigabatrin alone, reported retrospectively and from spontaneous reports. It should be noted that the retrospective studies published cover a few cases of exposure to vigabatrin monotherapy, and do not report any congenital malformations (Hunt *et al.*, 2005; Fonager *et al.*, 2000; Wide *et al.*, 2004; Mawer *et al.*, 2010; Veiby *et al.*, 2014).

Among the pregnancies exposed to vigabatrin in polytherapy, concomitant administration of antiepileptics known for their malformative nature in most cases does not make it possible to conclude as to the role of vigabatrin in the occurrence of malformations.

Type of malformations

To date, the malformations observed after exposure *in utero* to vigabatrin alone affect different organs, not demonstrating a specific malformative profile from vigabatrin. Nevertheless, the very small number of cases reported do not make it possible to come to a final conclusion.

Dose-effect relationship

No study concerning the relationship between the vigabatrin dose and the risk of disorders in children exposed *in utero* has been identified.

NEURODEVELOPMENTAL RISK

To date, the data relating to the neurodevelopmental risk further to exposure *in utero* to vigabatrin alone are almost non-existent, not enabling a conclusion.

VISUAL FIELD ABNORMALITY

To date, the data published on the risk of visual field abnormality in 6 children exposed *in utero* to vigabatrin report the results of the eye tests only without formal diagnosis of visual field abnormality (Sorri *et al.*, 2005; Lawthom *et al.*, 2009). Also, the very small number of children examined does not provide for the potential risk to be evaluated properly. In addition, pharmacovigilance cases of visual field abnormality after exposure *in utero* were reported, however the lack of details and analysis for these cases does not make it possible to conclude at this time, and the pharmaceutical company needs to provide an accurate analysis of them. If, after reassessment, after re-assessment, treatment is required, this risk is therefore to be considered in the choice of treatment and should be taken into account for follow-up of the child in the event of exposure during the pregnancy.

ZONIZAMIDE

INTERACTIONS WITH HORMONAL CONTRACEPTION

In the clinical studies conducted on healthy subjects, in steady state, this treatment did not have an effect on the serum ethinyl-estradiol or norethisterone concentrations with a combined pill.

MALFORMATION RISK

Data in animals

Zonisamide is teratogenic in 3 animal species (mice, rats and dogs) and embryolethal in monkeys after administration during the organogenesis phase at maternal posologies and plasma concentrations similar or lower than the therapeutic levels in humans.

Clinical data - Overall frequency of malformations

The data currently available on exposure to zonisamide during pregnancy are limited (Tomson *et al.*, 2018; Hernandez-Diaz *et al.*, 2012; Kallen *et al.*, 2013; spontaneous reports). By emitting the hypothesis that the following are not included in the pharmaceutical company's pharmacovigilance data:

♦ data from registers since no malformations were reported;

♦ case of malformation identified in Terappel (since the cases of malformation in the pharmaceutical company's pharmacovigilance database come from the USA, Japan and Italy, but not France).

In total, 3 cases of malformation would be reported among the 143 pregnancies exposed to zonisamide monotherapy at least during the 1st trimester and collected prospectively (2.1%).

Clinical data - Type of malformations

By compiling the data collected prospectively and retrospectively, and without co-exposure to an antiepileptic known to be teratogenic, 10 cases of malformations were reported. They are mainly heart, central nervous system and limb defects. The proportion of central nervous system malformations appears high compared to the other types of malformations. Nevertheless, in the light of the very small number of cases, the lack of detail on the risk factors, other than concomitant antiepileptic exposure (such as the mother's history, alcohol consumption, exposure to other drugs or substances, etc.) and the prospective and retrospective data collection, these data must be considered with caution and cannot be used to conclude as to the malformative profile of zonisamide.

Clinical data - Dose-effect relationship

No study concerning the relationship between the zonisamide dose and the risk of disorders in children exposed *in utero* has been identified for zonisamide.

NEURODEVELOPMENTAL RISK

In the current state of knowledge, the clinical data relating to the neurodevelopmental risk further to exposure *in utero* to zonisamide alone are almost non-existent, not enabling a conclusion.

ANTHROPOMETRIC PARAMETERS

Concerning growth retardation, the study looking at the anthropometric parameters of children exposed *in utero* to zonisamide monotherapy (Hernandez-Diaz *et al.*, 2014) report a statistically-significant reduction in birth weight and size, and a statistically-significant increase in small for gestational age (SGA) cases compared to the children exposed *in utero* to lamotrigine (RRa = 2.0 (1.2 − 3.6) by only analysing non-smokers) or not exposed to antiepileptics (RRa = 2.2 (1.1 − 4.4)). In addition, there is pharmacological plausibility since weight loss or absence of weight gain was observed in the patients treated (adults and paediatric population) in the clinical studies with zonisamide. If, after reassessment, treatment is required, this risk is therefore to be considered in the choice of treatment and justifies, in the event of exposure during the pregnancy, close monitoring of foetal and maternal weight (from the start of the pregnancy) and nutritional supplementation or increased calorie intake if necessary.

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It should be noted that the definition of autism spectrum disorders has evolved over time:

♦ Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; 1994): Pervasive developmental disorders (PDD) was distinguished in five subgroups:
a) Autism
b) Rett's syndrome
c) Childhood disintegrative disorder
d) Asperger's syndrome
e) Pervasive developmental disorders not otherwise specified (PDD-NOS)

♦ In last version of DSM-V (2013), four of these subgroups (Autism; Asperger's syndrome; Childhood disintegrative disorder; PDD-NOS) have been replaced by a general category "Autism spectrum disorders" (ASD). Rett's syndrome is no longer part of the classification system. DSM-V no longer distinguishes between these different sub types, all of which are now diagnosed ASD.

♦ International Classification of Diseases (ICD-10 – World Health Organization) : the term "Pervasive developmental disorders" (F84) includes several diagnostic categories : Childhood autism (F84.0) ; Atypical autism (F84.1) ; Rett syndrome (F84.2) ; Other childhood disintegrative disorder (F84.3) ; Asperger syndrome (F84.5)

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