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3 Guideline on good pharmacovigilance practices (GVP)

4 Product- or Population-Specific Considerations III: Pregnant and 5 breastfeeding women

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P.III.A. Introduction

The need for guidance on pharmacovigilance specifically for the use of medicinal products in pregnancy is widely recognised. The use of medicinal products during breastfeeding is also an area in need of further pharmacovigilance guidance. Pregnant and breastfeeding women are considered vulnerable, or special populations, and in addition there are potential effects on the unborn child or breastfed infant. This needs to be considered in the wider context of women of childbearing potential: pregnancy may be unplanned, or treatment may be started at a young age or long before the woman is considering pregnancy, so the effects of the medicine on pregnancy and the need to avoid pregnancy or for pre-conception counselling may have to be taken into account by the prescribing physician and the patient in these contexts.

Except for situations where a medicine used during pregnancy specifically aims to benefit the (unborn) child, risk-benefit considerations regarding the medicine use before or during pregnancy or breastfeeding differ from other medicine use. This is because, in addition to the benefits and risks of the medicine for the woman, the potential risks to the (unborn) child also need to be taken into account. In the case of pregnancy, the risks to be considered include not only those from exposure to the medicine when used, but also the risks of untreated disease for the woman and the unborn child when no medicine is used. In the case of breastfeeding, the benefits of breastfeeding need to be weighed against the risks to the infant from medicine exposure through breast milk, and any effects of medicine use on breast milk production also need to be considered.

Safety data obtained in the pre-authorisation phase are limited, due to the restrictions of clinical trials in terms of size, time and duration of follow-up and the inclusion and exclusion criteria for selecting participants. Safety data for special populations are even more limited. Once a product is placed on the market, if use in pregnancy and/or during breastfeeding is likely to occur, data collection to obtain a better understanding of risks associated with such use and to identify and characterise risks is important even where no safety concerns have arisen in the pre-authorisation phase. Whereas historically, obtaining data from pregnant women on medicine use and outcomes during the post-authorisation phase has been challenging, it is becoming increasingly feasible to access data and generate knowledge on safety in this population.

Increased and adequate data collection and data assessment in a timely manner will enable that patients and prescribers have relevant information to make informed decisions about using medicines during pregnancy or breastfeeding and that they are well-informed about uncertainties. The guiding principle is to keep adverse outcomes associated with medicine use during pregnancy and breastfeeding to a minimum, without unnecessarily withholding useful treatment options from pregnant and breastfeeding women.

This Product- and Population- Specific Considerations Chapter P.III of the Good Pharmacovigilance Practices (GVP) aims to provide guidance to marketing authorisation applicants/holders, competent authorities of Member States and the Agency for facilitating appropriate pharmacovigilance for medicinal products that may be used in pregnant or breastfeeding women.

In spontaneous reporting, the term 'adverse event' is synonym to (suspected) adverse reaction and all birth defects are (suspected) 'serious adverse reactions' (see GVP Annex I). In this GVP P.III., the term 'pregnancy outcome' refers to the result of a pregnancy and hence may be a serious adverse reaction (see P.III.A.2.); this is different from general pharmacovigilance terminology in which the term 'outcome' refers to the result of an adverse reaction.

Taking into account that the general guidance on pharmacovigilance processes in the European Union (EU) is provided in GVP Modules I to XVI, the guidance in this GVP P.III aims at integrating

pharmacovigilance, including risk management, and considerations for pregnant and breastfeeding women with the applicable structures and processes for pharmacovigilance overall. GVP P.III applies in conjunction with the GVP Modules I to XVI and does not replace these GVP Modules or introduce regulatory requirements in addition to those already covered in existing Modules.

In addition, the following guidelines should be consulted:

- CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005)[1];
- CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005)[2]; and
- ICH-S5 (R3) Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals[3].

The effects of medicines on fertility and the use of medicines in neonates are out of scope of GVP P.III; guidance on these areas is provided in GVP Module V on risk management planning and GVP Chapter P.IV on the paediatric population.

In this Chapter, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

P.III.A.1. Pharmacovigilance aspects specific to the use of medicinal products in pregnant or breastfeeding women

P.III.A.1.1. Availability and interpretation of data

Because pregnant women are rarely included in clinical trials, at the time of marketing authorisation, assessment of potential risks associated with the use of medicinal products in pregnancy usually relies on the extrapolation from non-clinical data and on knowledge of adverse embryo/foetal reactions of other products with similar pharmacological properties. There are many examples where the mechanism of action of the medicine is related to the mechanism of teratogenicity or adverse embryo/foetal reaction, and hence pharmacological-toxicological class effects have been observed. Consequently, when assessing potential risks for an active substance, known adverse pregnancy outcomes for another substance of the same class of medicinal products should be carefully considered. However, evidence of absence of harm to the child for one substance cannot be extrapolated to other substances of the same class and be interpreted as indicating the absence of a potential risk for these other substances. Exposure through semen is another route of exposure to the embryo or foetus. Whether this carries a risk in clinical practice is unknown at present, but this should be considered for highly teratogenic substances that are transmitted into semen.

Like pregnant women, breastfeeding women are usually excluded from clinical trials; therefore the estimation of risks for breastfed infants at the time of marketing authorisation may be based on pharmacokinetic (PK) data, on data about the severity of potential adverse reactions to the medicine in the user population, or data from experience with other products with similar pharmacological properties.

[1] www.ema.europa.eu
[2] www.ema.europa.eu
[3] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5/S5-R3EWG_Step2_Guideline_2017_0705.pdf

P.III.A.1.2. Adverse events related to physiological changes of pregnancy

Physiological changes during pregnancy may result in changes to medicine plasma levels and associated dose-related adverse reactions or under-treatment, either of which could have negative consequences on the pregnancy outcome through their impact on maternal health.

Additionally, for products with a narrow therapeutic window, adverse reactions or fluctuations in plasma levels known to occur in the general patient population treated with this medicine may have added or specific relevance during pregnancy due to exacerbated effects associated with physiological changes of pregnancy. In practice, availability of specific data on these phenomena is limited, and generating such data may be difficult when the terms of marketing authorisation are such that the product information advises not to use the medicine during pregnancy.

P.III.A.1.3. Susceptible periods and adverse pregnancy outcomes

Susceptibility to interference from medicine exposure resulting in adverse pregnancy outcomes varies at the different stages of embryonic and foetal development. The impact of *in utero* medicine exposure depends on the ability of a medicine to cross the placenta, dose and duration of such exposure as well as the gestational age at which the exposure occurs (taking into account a product's PK half-life). Clinically, gestational age is usually calculated from the last menstrual period, but more accurately established from ultrasound diagnostics[4]. Possible negative consequences of exposure include early pregnancy loss, births defects (teratogenicity), foetotoxic effects, adverse events on the neonate and delayed adverse events on the developing child (see P.III.A.2.). The timing of exposure impacts as follows:

- Gestational week 0-4: interference in the first two weeks after conception may result in early pregnancy loss;
- Gestational week 4-16: organogenesis occurs and can therefore be interfered with, resulting in major birth defects. However, each congenital abnormality has its specific critical period, e.g. neural tube defect between the gestational days 29 and 42 (i.e. between days 15 and 28 post-conception);
- Gestational week 16 to delivery: during the remainder of embryofoetal development, although structural anomalies may also occur, interference mostly causes minor anomalies, impacts on growth or results in transient or permanent functional defects such as neurodevelopmental disorders;
- Late pregnancy or during delivery: there is the potential for irreversible or reversible physiological impacts on the neonate. These particularly include premature closure of the ductus arteriosus, acute renal insufficiency or withdrawal reactions;
- Throughout pregnancy: interference through exposure to environmental agents, including medicines, may result in pregnancy loss or stillbirth.

It needs to be recognised that if a major teratogen mostly results in spontaneous pregnancy loss or stillbirth, then only evaluating the frequency of birth defects would underestimate the teratogenic impact. In epidemiology, this phenomenon is referred to as 'competing endpoints'. Further, if a product causes birth defects through interference with organogenesis, exposure to it may also have a developmental impact later in pregnancy and the perturbed development *in utero* may have

[4] This refers to clinical definition of gestational age; embryologists and toxicologists use time from conception (which may be important when considering clinical data in the context of non-clinical data).

developmental consequences for the child. Some adverse pregnancy outcomes only become apparent long after exposure has occurred, as the child develops, irrespective of when the exposure occurred. Adverse pregnancy outcomes can therefore not be evaluated in isolation, and this needs to be accounted for in any evaluation or study design.

Overall, birth defects that are visible at birth are relatively frequent at around ~3% of all live births; however, the frequency of each individual birth defect is considerably lower (and has been reported as ranging from 1 in 700 to 1 in 30 000 live births, or less). If a product is harmful *in utero*, it is unlikely to cause a detectable increase in the frequency of *all* birth defects. Instead, the frequency of some specific, but not all birth defects, may increase. Typically, in the population of pregnant women there are limited numbers of exposure to a medicine; therefore, there will be an even smaller number of adverse pregnancy outcomes (i.e. 'adverse events of special interest' for data collection and analysis). This has implications for the numbers of spontaneously reported adverse events and on cases identified through post-authorisation surveillance methods, as numbers are expected to be small, making it difficult to identify an increase in cases of a rare adverse reactions. It also means 'birth defects' in general should not be studied as one single outcome (P.III.B.4.).

P.III.A.1.4. Adverse events in the child following exposure through breastfeeding

Adverse events following exposure to medicines through breastfeeding identified so far are mostly immediate effects on the child (e.g. sedation, irritation, gastro-intestinal disturbances). For medicines excreted in breastmilk, especially for products with a long half-life, there will be a risk of accumulation in the infant if the ingested quantity is larger than the infant's capacity for metabolising and excreting the medicine. The risk to the child can be different depending on whether the mother takes a single dose or a few doses, or is under chronic treatment with the medicine, and whether she took the medicine already during pregnancy or initiated treatment during breastfeeding. PK data of a product in breast milk can help inform the level of exposure from breastfeeding. PK data in a child after intake of a medicine with breast milk provides some information about the possible risk to a child, and when an adverse reaction is suspected in a breastfed infant, it may be valuable to obtain a blood sample from the child. For more information on adverse reactions in neonates and infants see GVP Chapter P.IV.

P.III.A.2. Terminology

Terms for defining the foetus at the different stages of the pregnancy are:

Zygote: The single diploid cell formed from the fusion of the ovum and spermatozoon.

Pre-embryo: The first stage of prenatal (see below under 'Foetus') development from conception until the end of implantation in the uterus and the start of organogenesis, i.e. until the postconceptional day 15 or gestational day 29.

Embryo: The second stage of prenatal development including the organ-forming period (i.e. organogenesis) between gestational day 29 (beginning at 4 completed weeks of gestation) and gestational day 84 (i.e. the ending at 12 completed weeks of gestation).

Foetus: This term has two meanings; the narrow definition of foetus reflects the stage of foetal development after organogenesis until the birth, while the broad definition of foetus covers the whole prenatal development from the conception until the birth.

Terms for defining pregnancy outcomes[5] are:

Pregnancy outcome: End result of pregnancy, which includes ectopic pregnancy, miscarriage, foetal death, termination of pregnancy and live birth.

Ectopic pregnancy: Extrauterine pregnancy, most often in the fallopian tube.

Foetal death (intrauterine death, in utero death): Death prior to complete expulsion or extraction from the mother of a foetus, irrespective of the duration of pregnancy. Early foetal death (before 22 completed weeks of gestation) is known as miscarriage, whereas late foetal death (after 22 completed weeks of gestation) is known as stillbirth.

Miscarriage: Spontaneous abortion and molar pregnancy.

Termination of pregnancy (induced abortion, elective abortion): Artificial interruption of pregnancy for any reason.

Live birth: Complete expulsion or extraction from the mother of a foetus, irrespective of the duration of the pregnancy, that, after such separation, breathes or shows any evidence of life.

Gestational age: Measure of the age of a pregnancy calculated from the first day of a woman's last menstrual period or as estimated by a more accurate method such as ultrasound. The method used needs to be clearly stated in any reporting. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).

Birth weight: Initial weight of the infant at birth.

Pre-term birth (premature birth): Birth at less than 37 completed weeks (less than 259 days) of gestation.

Term birth: Birth at any time from 37 to less than 42 completed weeks (259 to 293 days) of gestation.

Post-term birth: Birth after 42 completed weeks of gestation or more (294 days or more).

Low birth weight: Body weight of the newborn at birth of less than 2,500 grams (up to and including 2,499 g).

Very low birth weight: Body weight of the newborn at birth of less than 1,500 grams (up to and including 1,499 g).

Intrauterine growth retardation (IUGR) ('small for gestational age'): Observed weight of a live born infant or size of a foetus lower than expected, usually below the tenth percentile, on the basis of gestational age.

Foetotoxic effect: Alteration of foetal growth, functional defects or malformations caused by a medicine or other substance and which may be transient or permanent.

Withdrawal syndrome: Syndrome, i.e. a set of symptoms of variable degree of severity, which occur on stopping or reducing, in dose or frequency of intake, the use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/or in high doses. The syndrome may be accompanied by signs of physiological disturbance. A withdrawal syndrome is one of the indicators of a dependence syndrome. Withdrawal syndrome can occur in neonates whose mother used psychoactive substances just before delivery.

[5] According to WHO-ICD 10, see https://icd.who.int/en/; national regulations might be different

Terms for defining congenital anomalies (birth defects) are:

Congenital anomaly: Morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay. Both onset and diagnosis of congenital anomalies can be delayed.

Congenital abnormality (structural birth defect, sometimes congenital malformation, foetal defect): A consequence of error of morphogenesis, i.e. structural-morphological defect, grossly or microscopically present at birth whether detected at birth or not.

Congenital malformation: A morphological defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process.

Isolated congenital abnormality: A single localised error of morphogenesis.

Multiple congenital abnormalities: A concurrence of two or more different morphogenetical errors, i.e. component congenital abnormalities in the same person.

Teratogen: A medicine or other environmental factor that can cause congenital abnormalities.

Major anomaly: A life-threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment. The prevalence of major abnormalities recognised at birth among live-born infants is 2%-4% in most series published.

Minor anomaly: Relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.

Prevalence: Number of instances of an occurrence in a given population at a designated time. For convenience these rates are usually multiplied by 1000 or 10,000 to avoid small decimal numbers. The numerator is the number of cases of the subject of interest. The denominator is the population from which the numerator came. The calculations below are intended to include all causes of the adverse event (i.e. without prejudice regarding causality) and they should include exposures to monotherapy as well as to multiple medicines. Accordingly:

$$\textbf{\textit{Live birth prevalence rate}} = \frac{\text{Number of cases among live born infants}}{\text{Total number of live born infants}} * 1000$$

$$\textbf{\textit{Birth prevalence rate}} = \frac{\text{Number of cases among live and stillborn infants}}{\text{Total number of (live + still) born infants}} * 1000$$

$$\textbf{\textit{Total prevalence rate}} = \frac{\text{Number of cases among live births, stillborn and terminated pregnancies}}{\text{Number of live births, stillbirths and terminated pregnancies}} * 1000$$

P.III.B. Structures and processes

P.III.B.1. Risk management plan

Depending on the available evidence for the product in the areas of pregnancy and breastfeeding, the risk management plans (RMPs) will reflect the measures considered necessary to identify, characterise and minimise a medicinal product's important risks, as described in GVP Module V. Further, GVP Module V states that "if the product is expected to be used in populations not studied and if there is a

scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information in the RMP." This statement is applicable to pregnant and breastfeeding women, as they are rarely included in clinical trials (see P.III.A.1.1.).

For products with anticipated use in women of childbearing potential there is a need to reflect the current understanding of safety in pregnancy and/or breastfeeding in the summary of the safety specifications in the RMP as follows: relevant knowledge gaps regarding risks associated with the use in pregnancy and/or breastfeeding should be included as missing information; data from non-clinical toxicity testing, observations in the pre-authorisation phase or from products from the same pharmacological class, as well as signals arising in the post-authorisation phase may result in describing important potential risks or important identified risks. For all three categories of safety concerns, recognition in the summary of safety specifications usually implies that additional pharmacovigilance activities for data collection and/or risk minimisation measures may be needed (see GVP Modules V and XVI).

The RMP should specifically discuss the likelihood of use of the medicine in pregnancy, breastfeeding and women of child-bearing potential in the light of the indications, alternative treatment options, the need for effective contraception and the complexities of changing treatment if use during pregnancy is to be avoided.

Rates of adverse pregnancy outcomes in women with specific underlying conditions may differ from baseline rates in the general population. Given that such specific underlying conditions may be the indication for prescribing, the background rates of adverse pregnancy outcomes in the target populations may need to be specified in the RMP, since such information has implications for the choice and interpretation of post-authorisation surveillance methods. For example, women with diabetes have a higher risk of giving birth to a child with macrosomia and women with heart disease may have an increased risk of giving birth to a child with congenital heart defects due to genetic predisposition. This needs to be covered in the 'populations not studied' section of the RMP.

Potential risks should be assessed based on findings from standard non-clinical studies, clinical data and epidemiological data on the product or related products. This evaluation should inform what, if any, further studies and analyses are needed for the adverse events of special interest as well as for any associated risk minimisation measures (RMM) to be implemented. The RMP also includes the RMM to be implemented and guidance for these is provided in P.III.B.7.

P.III.B.2. Management and reporting of adverse reactions

Spontaneous reporting during the post-authorisation phase is one primary source of information on adverse reactions occurring following exposure *in utero* or during breastfeeding. Reports where the embryo or foetus may have been exposed to (a) medicinal product(s) (either through maternal exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth.

It is essential that marketing authorisation holders and competent authorities in Member States collect and provide as many elements as possible for all cases, irrespective of whether or not a product is authorised for use in pregnancy or breastfeeding, to facilitate the evaluation. Appendix 1 of this GVP P.III lists information that could be collected; elements in this Appendix that are not captured in the ICH-E2B message format (see GVP Annex IV) of the individual case safety report (ICSR), if available, should be provided in the case narrative.

The requirements for the management and reporting of suspected adverse reactions from spontaneous reporting or other sources are described in GVP Module VI, including specific, detailed guidance regarding the way of ICSR reporting, such as for the items listed below:

- Coding of reports of use a medicinal product during pregnancy or breastfeeding as follows:
  - for the suspected adverse reaction, comply with the latest version of guidance for MedDRA Users, MedDRA Term Selection: Points to Consider (see GVP Annex IV – MedDRA support documentation);
  - for the route of administration, code, in the case of exposure in pregnancy leading to pregnancy loss or other adverse pregnancy outcomes, the route of administration as 'transplacental' and use the MedDRA term 'exposure in utero' in the Reaction/event section; and in the case of exposure during breastfeeding, code the route of administration as 'transmammary' and use the MedDRA term 'Drug exposure via breast milk' in the Reaction/event section. The route of administration for the mother should be coded in the data elements, parent section of the parent-child report;
- Coding outcomes of exposure during pregnancy is open to ambiguity as a record of 'exposure during pregnancy, resolved' may mean that there is a prospective report of pregnancy exposure and either exposure discontinued, or the pregnancy has ended. Without reporting any further information regarding the pregnancy outcome this is not helpful. Efforts must be made to report the pregnancy outcome, even if this is not known until long after the exposure occurred and irrespective of whether or not the exposure was discontinued during the pregnancy;
- If a birth defect is the indication for using a particular medicine, this should be reflected in the data element for indication (or medical history of the child) and not result in a parent-child report;
- Collecting and assessing information on off-label use and potential harm.

As many specific data elements as are possible to be obtained should be included in the structured ICH-E2B data elements of the ICSR (see GVP Annex IV) as well as the narrative. In addition, to evaluate a possible causal relationship between the exposure to the medicinal product and the adverse events reported, the following guidance should be adhered to:

- The type of report on use of a medicinal product during pregnancy or breastfeeding, which may be retrospective or prospective, needs to be specified in the narrative. Prospective data of pregnancy exposure are data acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital anomaly at prenatal examination (e.g. foetal ultrasound, serum markers). For prospective cases, the gestational age at first contact with a reporter should be reported in the narrative. Prospective reports should be followed up upon first reporting as well as upon the expected date of delivery for details of pregnancy outcome as well as for any follow-up information for the reported maternal adverse reactions. Retrospective data of pregnancy exposure are data acquired after the outcome of the pregnancy is known or after the detection of a birth defect on prenatal test.
- Gestational age when the suspected adverse reaction was observed in the foetus and the gestational age at time of exposure need to be reported as accurately as possible. Both may be provided in months, weeks, days or trimester. Gestational age should be preferably calculated from early foetal ultrasound. The method used to assess gestational age should be specified in the narrative. Information on the exposure to any medicinal product should be included in the ICH-E2B section 'Drug information' of the ICSR. Information on the exposure to other teratogens (e.g. infections, occupational exposures) and on other potential causes for the adverse pregnancy

outcome (e.g. familial history of congenital anomaly, maternal disease, lifestyle factors) should be included in the 'relevant medical history and concurrent conditions of parent' for so called parent-child reports, or in the patient's 'relevant medical history and concurrent conditions' in the report containing information on using drug during pregnancy.

- The results of examinations performed (e.g. foetal ultrasound, amniocentesis, laboratory tests) should be included in the section 'Results of tests and procedures relevant to the investigation of the patient' (see GVP Module VI).

Specific requirements for the submission of ICSRs with pregnancy exposure are outlined in GVP Module VI and are summarised in Table P.III.1. as follows[6]:

Table P III.1.: Requirements for the submission of individual case safety reports with pregnancy exposure

1st situation:	**Adverse reactions reported both in mother and**	
	Spontaneous abortion	1 case ‹‹mother››
	Foetal death without information on malformation	1 case ‹‹mother››
	Foetus with defects	2 cases: 1 case ‹‹mother›› and 1 case ‹‹foetus›› but cases linked (see section A.1.12 for ICH-E2B(R2) or C.1.10 for ICH-E2B(R3))
	Birth defects or adverse reaction in baby	2 cases: 1 case ‹‹mother›› and 1 case ‹‹baby›› but cases linked (see A.1.12 ICH-E2B (R2) or C.1.10.r for (ICH-E2B(R3))
	No adverse reaction in child	1 case ‹‹mother››, explicitly stating the pregnancy outcome
2nd situation:	**No adverse reaction in mother and**	
	Spontaneous abortion	1 case ‹‹mother››
	Foetal death without information on malformation	1 case ‹‹mother››
	Foetus with defects	1 case ‹‹foetus››
	Birth defects or adverse reaction in baby	1 case ‹‹baby››
	No adverse reaction in child	No case[7]
Particular situation:	**Twins**	1 case for each twin with an adverse reaction, the individual cases should be linked (see A.1.12 ICH-E2B(R2) or C.1.10.r for ICH-E2B(R3))

P.III.B.3. Periodic safety update report

The requirements for periodic safety update reports (PSURs) are detailed in GVP Module VII. The evaluation of data in the PSUR may be one way of further characterising risks of medicine use during pregnancy and breastfeeding. In addition, in line with the guidance in GVP Module VII the following applies:

[6] Copied from Annex 2 of the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data, www.ema.europa.eu

[7] Although not meeting the criteria for adverse reactions and hence no requirement for reporting as ICSR to EudraVigilance, for products that are not authorised for use in pregnancy the numbers of exposed cases reported prospectively, where no adverse reaction is reported in the mother or child and where a healthy baby is born, should be reported in PSURs as 'exposure during pregnancy', along with relevant data from other sources.

- The PSUR needs to summarise the relevant safety information from spontaneous ICSRs of adverse pregnancy outcomes, or adverse reactions/outcomes in the child following exposure *in utero* or during breastfeeding, ICSRs published in the medical literature and post-authorisation studies (PASS) ongoing or finalised during the reporting interval (P.III.B.4.).

- Age- and sex-specific drug utilisation data need to be included (in PSUR section 'Estimated exposure and use patterns'), which allows for an understanding of the extent to which the product is being used in women of childbearing age and pregnant or breastfeeding women. Available information regarding cumulative numbers of exposed patients and the method of exposure calculation should be provided. Sources of exposure data may include non-interventional studies, registries, and formal drug utilisation studies in pregnant/breastfeeding women.

- Safety during pregnancy and breastfeeding should also be described for products where adverse pregnancy outcomes or adverse events associated with breastfeeding is a safety concern (important risk or missing information) specified in the PSUR and/or the RMP, but it is encouraged also for products where these outcomes/events are not specified as a safety concern. This information on safety may come from dedicated, non-interventional studies, and in such cases, findings should be presented in PSUR section 'Findings from non-interventional studies'. Occurrence of spontaneous reports of adverse pregnancy outcomes should be presented in the PSUR section 'Signal and risk evaluation'.

- Data coming from an ongoing or finalised observational study, e.g. a pregnancy registry, should be analysed as per the milestones agreed in the RMP and the analyses should be discussed in the PSUR, as detailed in the guidance on registries in section 5.2.3 of the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005)[8].

P.III.B.4. Post-authorisation safety studies

The requirements for the design and conduct of post-authorisation safety studies (PASS) in GVP Module VIII should be followed, as well as the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005)[9]. For medicines where safety data relating to use of a medicine in pregnancy and breastfeeding are limited, additional pharmacovigilance activities may be warranted (see P.III.B.1.) to better characterise potential risk with use of the product in pregnancy and breastfeeding. Marketing authorisation holders and competent authorities are required to consider whether a PASS would be an appropriate tool for this purpose. A PASS may constitute a drug utilisation study or it may investigate specific risks to the embryo, foetus or child. Potential study designs for the latter include all epidemiological designs in principle, including but not limited to pregnancy registries (see P.III.B.4.2.1.).

As per general guidance, the decision on whether or not to include additional pharmacovigilance activities in the RMP should be taken in a risk-proportionate manner. Considerations regarding risk proportionality will differ between the populations of pregnant women and breastfeeding women because the consequences of harm differ between these populations. In situations where a medicine is harmful to the child but use for the mother is imperative, it is relatively uncomplicated to avoid harm to the child during breastfeeding whereas avoidance of harm during pregnancy is not as straightforward.

[8] www.ema.europa.eu
[9] www.ema.europa.eu

Carrying out a PASS may be of particular value when use of a medicine is expected in pregnancy or breastfeeding, such as in the following situations:

- when use of the product cannot be discontinued during pregnancy due to the disease being treated, when a disorder arises during pregnancy that needs treatment, or where changes in treatment during pregnancy are associated with risks for the pregnant woman and/or the foetus;
- if a potential risk to the child has been suggested by non-clinical data, a signal (see P.III.B.5.) or based on the chemical or pharmacological properties of the medicine;
- where the medicine is used to treat conditions that occur commonly in women of child-bearing potential; or
- if measuring compliance with RMM in place regarding pregnancy or breastfeeding (e.g. in the product information, educational material or a pregnancy prevention programme) (see P.III.B.7.) is needed.

If a PASS is considered warranted, it should be designed taking into account the issue of competing endpoints (see P.III.A.1.3.) as well as the fact that exposure at different gestational ages may be associated with different adverse outcomes. The evaluation should consider all relevant outcomes throughout the human developmental lifecycle, therefore, and capture data on exposure *in utero* as well as any additive adverse events of medicine exposure through breast milk. The child should be followed up for a long enough period to capture the relevant information on health or developmental impact.

Possible ethical and feasibility aspects specific to the use of medicines in pregnancy or breastfeeding should be adequately anticipated and managed in the study protocol. Inclusion of pregnant women in a PASS should be solely subject to the clinical decision to treat the woman for her medical condition.

P.III.B.4.1. Pharmacokinetic studies on pregnancy-related physiological changes

If use of a medicine during pregnancy is indicated and from all available evidence, there is no suggestion of harm, it may be appropriate to evaluate the impact of pregnancy on medicine plasma levels in pharmacokinetic (PK) studies; sometimes, it is suggested that free rather than total medicine plasma levels are monitored in pregnant women. Such studies aim to inform on dose adjustments arising from changes in plasma levels affected by pregnancy related physiological changes. Examples include some anti-human immunodeficiency virus (HIV) products, where under-treatment may result in enhanced vertical viral transmission; diabetes or asthma treatment, where good disease control in the mother enhances the likelihood of a healthy child; or products with a relatively narrow therapeutic window, where higher plasma levels may increase the risks of adverse reactions in the mother and lower plasma levels may diminish efficacy.

P.III.B.4.2. Epidemiological studies

A rationale for the appropriate study design to address safety concerns relating to use of the medicinal product in pregnancy and/or breastfeeding should be provided in the study protocol. Study types by objective include:

- drug utilisation studies: descriptive studies to establish the extent of exposure in women of childbearing potential, pregnancy and breastfeeding women, as well as utilisation/ switching/discontinuation patterns and time trends , including evaluation of user characteristics such as folic acid use, smoking, alcohol intake, other lifestyle factors, body mass index, medical

conditions that could lead to adverse embryogenic, foetal or neonatal outcomes, and exposure to known teratogenic or foetotoxic medicines;

- medicines safety studies: pharmacoepidemiological studies of adverse events of special interest in causal association with a medicine, taking into account the impact of the underlying maternal condition (i.e. non-exposed disease comparison group) and other potential confounders;
- Studies to evaluate the effectiveness and broader impact of RMM.

Depending on the product characteristics and the context of use, in some cases (e.g. when use in pregnancy is expected and further characterisation of associated risks considered necessary) it may be appropriate to initiate a safety study at the time of marketing authorisation. In other cases, if a drug utilisation study were to show usage in women of childbearing potential or in pregnant women to an extent that studying associated pregnancy outcomes would be warranted, then setting up a PASS with safety endpoints should also be considered. Likewise, a signal (see P.III.B.5.) could lead to a request for a study to examine the extent of use and put the number of spontaneously reported suspected adverse reactions into perspective. The decision on whether and if so, what studies are needed to evaluate specific pregnancy outcomes (see P.III.A.2.) should be guided by reproductive toxicity studies, signals from spontaneous reports or other sources, or the understanding of risk in the pharmacological class. Finally, drug utilisation studies can also be designed to show change in use over time with implementation of RMM in specific populations.

Preferably and if feasible, epidemiological studies should be carried out using existing data sources (i.e. secondary data use) and be designed in such a way as to minimise bias and confounding (see P.III.B.4.2.3.). Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.III.A.1.3.), it is usually necessary to include participants from more than one country in order to achieve adequate power.

P.III.B.4.2.1. Pregnancy registries

If additional pharmacovigilance activities in the form of data collection from a pregnancy registry are justified, the following should be considered:

- Registries that, in principle, aim to capture all pregnant women with the disease are generally more useful than medicinal product-specific registries because they provide for longitudinal study of treatment and effects (including switches between products) throughout pregnancy, comparison between products and pregnancy outcomes in an unexposed population;
- In exceptional cases, a medicinal product-specific pregnancy registry may be appropriate;
- The use of existing (pregnancy) registries or databases should be considered to enhance long-term follow-up, facilitate the inclusion of comparator groups, make use of existing infrastructure for data collection and analysis, to avoid unnecessary duplication of effort and enhance efficiency in general;
- It may therefore be prudent to opt for a hybrid study design in which the product-specific information required from the marketing authorisation holder is complemented with public data sources such as birth defects registries, data captured by the teratology information services, or data captured in electronic health records. Useful information may be acquired and study feasibility may be enhanced by combining existing data sources with de novo data collection regarding use of a specific medicinal product in pregnancy;

- Registries should be inclusive rather than exclusive by means of comprehensive inclusion criteria. Although retrospective enrolment may introduce bias, information entry after the pregnancy outcome is known can still be valuable. Therefore, although prospective enrolment is preferred and should be encouraged, women who wish to enrol retrospectively should not be discouraged to do so and their pregnancy outcomes should be included in the study report. The retrospective nature of such data needs to be accounted for in the analysis;
- Follow-up may include longer-term evaluation of neonates or infants for developmental maturation. In such cases and if the active substance is present in breastmilk, it is considered useful to additionally include information regarding breastfed infants. The healthcare professionals who fill data in the registry should be encouraged to record whether the mother starts to breastfeed and if so, to ask the mother regarding possible adverse reactions in her infant at each visit;
- Information regarding the existence of a pregnancy follow-up activity should be included in any mandated pregnancy-related educational materials.
- The guidance for data collection on pregnancy exposure and outcomes in P.III Appendix 1 should be followed.

Further considerations on use of registries for regulatory purposes are available on the EMA Patient registries webpage[10].

P.III.B.4.2.2. Long-term pregnancy outcomes

Assessing the long-term impact of medicine use in pregnancy on the child is challenging, especially as some adverse health outcomes may not become apparent until many years after exposure. Generally, the decision as to whether or not to conduct studies into childhood needs to be based on biological plausibility and/or a combination of information from non-clinical data, clinical data (e.g. malformations, prematurity, growth retardation, foetal and neonatal outcomes), pharmacological properties, and signals regarding adverse long-term outcomes. For evaluating neurodevelopmental outcomes, the time required to develop motor and language skills (from rudimentary skills just after birth to fine motor or language skills later in childhood) mean that different measurements should be used at different ages.

Depending on the outcome of interest, follow-up may be into preschool or school age, and/or adolescence, as appropriate to reflect the neurodevelopmental outcomes mentioned. A complementary approach combining data from existing registries/databases and studies with primary data collection may be needed. A multidisciplinary approach involving epidemiological, paediatric, genetic and neurodevelopmental expertise is crucial.

P.III.B.4.2.3. Handling of bias and confounding

The design and conduct of a PASS in the population of pregnant women should take into account the specific characteristics of this population that may lead to confounding. When drug utilisation studies are being designed, it is useful to consider including information on such characteristics to aid the design of possible further safety studies; examples of potential factors of interest include lifestyle factors (e.g. smoking, alcohol intake, folic acid intake, body-mass index (BMI)) or other factors relating to foetal or neonatal development (e.g. maternal pregnancy complication, prior history of negative pregnancy outcomes or pre-term birth, prescription of known teratogenic or foetotoxic medicines, maternal disease likely to cause foetal or neonatal adverse consequences). Additionally, study design

[10] www.ema.europa.eu.

should consider misclassification errors that result from incomplete recording of diagnoses or exposure, such as recall bias, as well as limitations regarding identification of competing endpoints (e.g. pregnancy loss, elective termination, miscarriage); this should also be addressed in the protocol and interpretation of the results. Attempts to minimise selection bias should be made for example by ensuring a population-based approach such as through national birth cohorts.

Study design elements that enable less biased results include the use of different comparators, sibling designs, self-controlled designs and positive and negative controls (i.e. exposure before, but not during pregnancy, or exposures in different periods of gestation). These designs may not always be appropriate for the evaluation of medicinal products with a very long half-life.

Based on the guidance in P.III.B.4., for PASS in pregnancy, proposed study designs should specifically address and justify:

- the exposure windows to be studied;
- how gestational age will be determined;
- how challenges with competing endpoints will be handled;
- whether or not, apart from the product of interest, different exposures will be combined (e.g. all products in the same pharmacological class will be treated as one type of exposure, or they will be evaluated as different exposures); and
- which pregnancy outcomes and outcomes in the child will be evaluated;

The PASS protocol should also explain how the bias due to exposure misclassification, missing data, unmeasured confounding and outcome ascertainment as well as co-exposure effects will be handled.

P.III.B.4.3. Clinical lactation studies

In cases where no human data are available on the extent of medicine transfer into breast milk, where use by breastfeeding women is expected to be common, and based on the medicinal product's pharmacological properties, it is considered plausible that there is a risk to breastfed infants, a PK study amongst breastfeeding women should be considered. This is expected to be the case when a medicinal product is commonly used by women of reproductive age (e.g. antidepressants, anti-infectives, diabetes medications, pain medications), or when there is evidence of use or anticipated use of the medicinal product by lactating women.

Medicine concentration levels in breast milk samples should be measured and a relative infant dose calculated, to obtain information for supporting the risk assessment and provision of advice on timing of medicine intake relative to breastfeeding where this may be feasible (e.g. for short-term or single dose treatments). Moreover, data on the effect of the medicine on milk production or composition should be collected, if potentially clinically relevant.

So far, PASS in breastfed children are very rare. However, in the case of a medicine highly used in women who could breastfeed, with an unknown potential for serious adverse reactions in breastfed children, establishing safety information in the post-authorisation phase should be considered as an important source of information. This may include the clinical follow-up of breastfed children whose mothers are treated with a specific medicine. Pregnancy registries in which new-borns are further observed could include the collection of information on breastfeeding to allow a comparison of a group of breastfed children to those not breastfed and those breastfed in mothers who are not treated with the product of interest. In case a medicine is used during breastfeeding and questions arise regarding

a potential long-term impact on child´s growth, neurodevelopment, or other adverse events with a prolonged latency, it should be considered to carry out long-term follow-up in those children.

P.III.B.5. Signal management

Signal management activities of adverse pregnancy outcomes should be done in accordance with GVP Module IX. In addition, some of the challenges with signal detection on spontaneously reported adverse reactions in the post-authorisation phase that are specific to the population of pregnant women should be taken into account.

The identification of relevant cases plays an important role in supporting detection and validation of signals and consideration should be given to the types of adverse pregnancy outcomes searched for by designing an appropriate MedDRA search strategy. The Standardised MeddRA Query (SMQ) (1st level) 'Pregnancy and neonatal topics' may be useful to retrieve all pregnancy outcomes (such as congenital anomalies, spontaneous abortion, stillbirth, risk of labour complications), so that patterns of adverse outcomes may be recognised as signals for further risk assessment. It should be noted however that some outcomes, e.g. congenital malformations, are more likely to be detectable at birth and thus more likely to be reported in association with exposure *in utero*. Reactions with a delayed onset or a delayed diagnosis (for example those that do not involve visible anomalies, such as neurodevelopmental adverse effects) may be less likely to be reported in association with exposure in pregnancy.

In this phase of signal detection and verification, efforts should be made to confirm detailed information (e.g. timing of gestation, duration, product) regarding exposure during pregnancy. This can be done by identifying cases with the relevant information provided in the case reports (e.g. seriousness criterion 'congenital anomaly/birth defect', trans-placental route of administration, gestational age at time of earliest exposure) whenever available. In some situations, spontaneous reporting of suspected adverse reactions / pregnancy outcomes has helped to confirm suspicions of embryofoetal toxicity arising from non-clinical studies.

P.III.B.6. Safety communication

The general guidance in GVP Module XV on safety communication and communication-related aspects of GVP Module XVI on RMM should be followed, together with the considerations in this Section. In addition to the relevant sections of the guidelines referred to in P.III.A., the European Commission Guideline on the Summary of Product Characteristics[11] and the European Commission Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[12] are applicable. For communication regarding pregnancy for vaccines, GVP Chapter P.I should be applied too.

GVP Module XV provides an overview of different means of communication and stresses the importance of defining communication objectives. The specific communication objectives discussed for medicines which may be used by women who are of child-bearing potential, planning a pregnancy, or are pregnant or breastfeeding, relate to enabling women and healthcare professionals to take informed therapeutic decisions for preventing negative impact of maternal use of medicines on the child, preventing unnecessary pregnancy terminations, promoting adherence to RMM and supporting informed choices where the wish for a child exists.

Communication therefore needs to address the specific information needs of women and healthcare professionals in these different possible clinical scenarios. It is encouraged to also consider that monitoring news and/or social media directed at pregnant and/or breastfeeding women may provide

[11] https://ec.europa.eu
[12] https://ec.europa.eu

data for becoming aware of public concerns and be helpful for identifying frequent information needs to be addressed (see GVP Module XV).

The implementation of RMM in healthcare practice also requires specific communication skills in relation to risks and benefits of medicine use in pregnancy and related uncertainties, which may be more challenging than conveying risks of medicines in other circumstances. RMM targeted at healthcare professionals should provide them with information and tools in such a way that they will be able to effectively inform and discuss risks and RMM with their patients.

In order to provide for the above communication objectives, marketing authorisation holders and competent authorities are encouraged to address, in the product information and any additional RMM such as educational materials targeted at different audiences, the following in appropriate manner if information is available and applicable:

- Physiological changes during pregnancy that may result in changes to plasma levels and associated dose-related adverse reactions or under-treatment, either of which could have consequences on the pregnancy outcome through their impact on maternal health;
- Characterisation of the risks of adverse pregnancy outcomes and risks for the child in terms of the nature, severity, seriousness and frequency of potential adverse reactions; ideally this information is provided in relation to the magnitude of exposure (i.e. dose, duration, time period (i.e. gestational age or age of the breastfed child) and/or in relation to the time elapsed if exposure has already been discontinued);
- Magnitude of the absolute risks for adverse outcome(s)/reaction(s) as well as the background prevalence of birth/developmental defects in absolute numbers, making comparisons more immediately accessible to patients and healthcare professionals;
- Additional RMM, including pregnancy prevention programmes (PPP) and contraception advice (see P.III.B.7.);
- Presentation of potential risks of breastfeeding for the child in the light of benefits of breastfeeding itself if breastfeeding is not contraindicated, and advice on dose-reduction, timing of breastfeeding in relation to medicine intake, monitoring and early detection of adverse reactions on the child and when to seek medical advice;
- Management of adverse reactions in the child.

Communication should be tailored for addressing women/adolescent female patients and their partners, as well as parents or carers in the case of adolescent female patients, and healthcare professionals (including in particular general practitioners, paediatricians, obstetricians and gynaecologists, midwives, nurses and pharmacists).

P.III.B.7. Risk minimisation measures

In the area of pregnancy and breastfeeding, the objective of risk minimisation measures (RMM) generally is to reduce any risk to the child as much as possible given the need for appropriate treatment for the mother. In this area, strategies for RMM include those aiming at:

- Avoiding inadvertent exposure *in utero* (e.g. by pre-conception counselling, discontinuing a specific medicine when the wish for child exists or avoiding pregnancy through effective contraception), taking into account teratogenic properties and the half-life of the medicinal product (see P.III.B.7.2.);

- Mitigating the risk in the event of unplanned pregnancy by switching or discontinuing the medicinal product where possible (which may require specialist consultation) and intensified monitoring of the pregnancy;
- Modifying medication before or during pregnancy, e.g. by changing the dosage or route of administration or adapting treatment to the physiological changes in pregnancy for example in the case of medicines with a narrow therapeutic window;
- Where harm to the embryo or foetus by transfer through semen is an identified safety concern, minimising exposure via male partners exposed to the medicine by use of barrier contraception, avoidance of donation of sperm and informing the physician if the partner becomes pregnant;
- Minimising exposure through breast milk by optimised timing of medicine intake, short treatment duration, discontinuation of medication or if minimising exposure is not feasible or acceptable, avoiding breastfeeding. If the decision is taken to breastfeed whilst continuing maternal medicine intake and there is a (potential) risk for the child, the infant should be carefully monitored and breastfeeding discontinued in the case of the adverse signs and symptoms;
- In breastfeeding women, depending on the therapeutic context and the availability of therapeutic alternatives, avoiding use of medicines that significantly reduce breast milk production.

When serious risks of a medicinal product with use in pregnancy have been identified, a set of stringent RMM should be implemented aiming at avoiding exposure *in utero*, including sometimes a PPP (see P.III.B.7.2.). For less serious risks, the emphasis will be on ensuring that healthcare professionals and patients have information available supporting them making informed decisions regarding the most appropriate choice in the individual case.

P.III.B.7.1. Educational materials

Materials targeted at healthcare professionals and/or women of childbearing potential, pregnant or breastfeeding women (or parents/carers in the case of likely exposure of adolescent females) may be warranted as part of the RMP (see P.III.B.1.) if there are important identified or potential risks and routine RMM is not considered sufficient. The guidance in GVP Module XVI and its Addendum I as well as on communication in P.III.B.6. applies. Appropriate educational materials may cover:

- Information regarding the risks and/or uncertainties in relation to exposure *in utero* or through breastfeeding, the risks of the underlying medical conditions, considerations for women of child bearing potential to use adequate contraceptive measures, advice about dosing, switching or discontinuation of treatment, monitoring of the foetus/child or other RMM;
- Information for healthcare professionals to support their communication about risks and RMM with female patients (or their parents/carers);
- Information for women (considering) using the product that explains the risks and the need to consult their healthcare professional to establish the most appropriate treatment and monitoring options for them individually;
- Encouragement of healthcare professionals and pregnant women to report exposure and pregnancy outcomes or suspected adverse reactions in a (breastfed) child to, as appropriate, a pregnancy registry (possibly with follow-up into breastfeeding), teratology information centre, competent authority or marketing authorisation holder (with contact details provided).

The target healthcare professional population for educational material needs to be agreed in each particular case, taking into account the characteristics of the medicinal product and the disease as well

as the situation that different healthcare professionals may be involved in the care of long-term conditions during pregnancy. Different educational materials may be appropriate for different healthcare professional types and specialities.

Patient alert/reminder cards should provide succinct messages on the potential for harm, the need for contraception, action to take in the event of an unplanned pregnancy and action to take if planning a pregnancy, as applicable.

P.III.B.7.2. Advice on effective contraception

In cases where pregnancy should be avoided during the use of a product (according to section 4.3 or 4.6 of the summary of product characteristics (SmPC)), women of childbearing potential must be advised, through the package leaflet and possibly in addition through educational materials (P.III.B.7.1.), to use effective contraception. The decision on the contraceptive method should be an individual informed choice and may depend on a variety of factors including the duration of the indicated treatment.

Contraceptive methods have different efficacy as well as 'perfect use' and 'typical use' failure rates, due to different potential and rates of incorrect or inconsistent use or effects of interacting medicines. Risk of user error is higher for daily methods than for long-acting methods and is highest for methods used at time of sexual intercourse. Given the differences in efficacy and duration of effect, the need for pregnancy testing before and during use of a medicine differs between the contraceptive methods (see P.III. Appendix 2). Instructions should specify that pregnancy must be excluded before treatment initiation and each repeat prescription and for how long pregnancy must be avoided, taking into account the half-life of the product and/or its metabolites, the pharmacological effect, and for some genotoxic products, spermatogenesis and/or folliculogenesis.

For highly teratogenic substances, the potential of exposure through semen should be considered and if an identified safety concern for exposure through semen exists, the recommendation to use barrier methods needs to be made.

P.III.B.7.3. Pregnancy prevention programme

When a medicinal product with known teratogenic effect is intended for use in women of childbearing potential, implementing a pregnancy prevention programme (PPP) may be appropriate. Scenarios when a PPP may be needed include chronic conditions where treatment may be started long before the patient becomes of child-bearing potential or is considering pregnancy.

When considering the need for a PPP, one should take into account situations such as the product is indicated for use only in men and/or postmenopausal or otherwise infertile women, for the treatment of life threatening conditions, or for short term or single use of active substances with a short half-life.

The nature of the PPP will depend on the indication, the duration of use of the medicine, and whether or not alternatives to the medicine are available (e.g. delaying pregnancy, delaying treatment or using an alternative medication or other kind of treatment). The guidance to be followed for PPPs is provided in GVP Module XVI.

In relation to evaluating the effectiveness of PPPs, the following applies in addition to GVP Module XVI: In the case of a pregnancy occurring during the use of medicinal product for which a PPP is in place, the reasons for the occurrence of the pregnancy should be evaluated, where feasible, for the continuous improvement of the PPP. A formal root cause analysis should be considered if substantial

failures are identified. These efforts, and any action resulting from them, need to be reported routinely in the PSUR (P.III.B.3.).

P.III.C. Operation of the EU network

P.III.C.1. Submission of period safety update reports in the EU

For all teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the RMP or the PSUR, Table P.III.2. should be provided in the PSUR and filled in completely with reporting period interval and cumulative data. For all other products, reports on pregnancy outcomes in the list below should be provided as available. The congenital malformation rate amongst the exposed is estimated by considering pregnancy exposures at least during the first trimester, collected prospectively and for which the outcome of the pregnancy is known. Additionally, any neonatal adverse reactions and functional anomalies need to be captured. Overall malformation rates as well as the proportional prevalence of individual birth defects have to be compared with relevant reference prevalence rates and discussed, if relevant, by the marketing authorisation holder.

Table P.III.2.: Table for reporting numbers of individual case safety reports in periodic safety update reports[13]

Pregnancy outcome	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy										
Spontaneous abortion										
Elective termination (foetal defects)[14]										
Elective termination (no foetal defects or unknown)										
Stillbirth with foetal defects[14]										
Stillbirth without foetal defects										
Live birth with congenital anomaly[14]										
Live birth without congenital anomaly										
Total										

P.III.C.2. Post-authorisation safety studies in the EU

Several data sources in the EU are available for carrying out PASS, including drug utilisation studies, in pregnancy in the post authorisation phase, as compiled by the European Network of Centres for Excellence in Pharmacovigilance and Pharmacoepidemiology (ENCePP)[15]. They include regional or nationwide population-based medical databases, prescription databases, general practice databases, birth cohorts, congenital malformation registries, product- or disease specific pregnancy registries and exposure cohorts obtained through teratology information services. Additionally, an overview of all EU data sources available in principle for evaluation of long-term pregnancy outcomes, with details on content as well as governance, is available in the European Union electronic Register of Post-

[13] Copied from Annex 3 of CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005), www.ema.europa.eu

[14] The observed phenotype should be specified.

[15] http://www.encepp.eu/structure/documents/Data_sources_for_medicines_in_pregnancy_research.pdf

Authorisation Studies (EU-PAS Register)[16,17]. Reliable information regarding patient exposure in breastfeeding is not routinely available but may exist in some European birth cohorts.

Study protocols and results should be submitted to the competent authorities in the EU and made available through the EU PAS Register; the latter is an obligation on marketing authorisation holders for all imposed PASS (see GVP Module VIII) and encouraged for all other PASS.

[16] http://www.encepp.eu/encepp/studiesDatabase.jsp
[17] http://www.encepp.eu/encepp/viewResource.htm?id=27936

P.III. Appendix 1: Questionnaire to collect information on pregnancy exposure

This appendix is copied from the CHMP Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005) and provides a number of possible parental and neonatal data elements from which relevant points can be selected when establishing a questionnaire of pregnancy exposure to medicinal products. What is to be collected should be defined appropriately according to the specific condition / disease or exposure of interest. Not all data elements below are ICH-E2B data elements but a case narrative, if available, should reflect the relevant information. It is acknowledged that, in some instances, data may be difficult to obtain, but, in general, the more comprehensive the data collection, the more reliable will be the results.

A. GENERAL INFORMATION

- Prospective / retrospective case
- Date of initial contact with marketing authorisation holder
- Source of information ('reporter qualification' in ICH-E2B; a more specific description can be provided in the case narrative e.g. pregnant woman, primary care physician, obstetrician, paediatrician, other)
- Identification of reporter
- Additional identification of the gynaecologist-obstetrician (if reporter is the patient or the primary physician), and the address of the place where the mother plans to deliver

B. MATERNAL INFORMATION

- Identification of patient
- Date of birth (or age)
- Weight, height

Obstetrical history

- Number of previous pregnancies and outcome (live birth, miscarriage, elective termination with specification of gestational length and context, late foetal death, ectopic pregnancy, molar pregnancy)
- Previous maternal pregnancy complications
- Previous foetal/neonatal abnormalities and type
- History of subfertility

Maternal medical history

Risk factors for adverse pregnancy outcomes including environmental, occupational, substance abuse exposures and medical disorders such as hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS (specify viral load, CD4 count), and other, including other predisposing factors for neurodevelopmental disorders.

Current pregnancy

- Date of last menstrual period (LMP)
- Gestational age at the time of the first contact with MAH (specify if based on ultrasound or LMP)
- Gestational age at the time of drug exposure, preferably based on ultrasound and with the method of determining gestational age specified
- Estimated date of delivery
- Number of foetuses
- Treatment for infertility (specify)
- Exposure to products subject to medical prescription, OTC products, pregnancy supplements such as folic acid, multivitamins:

  ⇒ Name

  ⇒ Dosage & route

  ⇒ Date of first use, date of end of treatment, duration

  ⇒ Indication
- Use of tobacco, alcohol, illicit drugs (specify amount and if stopped during pregnancy)
- Results of serology tests, e.g. rubella, toxoplasmosis etc.
- Complications during pregnancy and date (including any adverse drug reactions)
- Disease course(s) during pregnancy and any complications
- Antenatal check-up (specify dates and results), e.g. foetal ultrasound, serum markers (AFP, other), chorionic villi biopsy (CVS), amniocentesis, non-invasive prenatal test

<u>Delivery</u>

- Mode of delivery
- Labour / delivery complications (foetal distress, amniotic fluid abnormal)
- Abnormal placenta

<u>Family history</u>

- History of congenital abnormality, psychomotor retardation in the family (specify paternal/maternal and relationship)
- Consanguinity between parents (specify degree)

C. PATERNAL INFORMATION if appropriate

<u>General information</u>

- Age or birth date

<u>Relevant medical history</u>

<u>Medical products exposure</u>

D. NEONATAL INFORMATION

Initial

- Source of information
- Date of receipt of information
- Outcome of pregnancy and date (ectopic pregnancy, molar pregnancy, miscarriage, elective termination, late foetal death and stillbirth, live birth)
- Date of birth
- Gestational age at birth
- Gender of neonate
- Results of neonatal physical examination including:

  ⇒ Weight at birth

  ⇒ Length, head circumference at birth
- Malformation/anomalies diagnosed in a foetus or at birth
- Conditions at birth (including Apgar scores at 1 and 5 minutes, need for resuscitation, admission to intensive care unit)
- Dysmaturity
- Neonatal illness, hospitalisation, drug therapies

Follow-up

- Source and date of information
- Malformation/anomalies diagnosed and (cyto)genetic testing results obtained since initial report
- Developmental assessment
- Infant illnesses, hospitalisations, drug therapies, breastfeeding

E. FOETAL INFORMATION in the case of elective termination, spontaneous abortion and late foetal death

- Source of information
- Date of receipt of information
- Reason for termination
- Gestational age at termination
- Results of physical examination (gender, external anomalies) and pathology

P.III. Appendix 2: Pregnancy testing and contraception for pregnancy prevention during treatment with medicines of teratogenic potential

Risk of pregnancy should be assessed prior to each teratogen prescription

- Risk of pregnancy may be high at start of a method or when switching between methods due to risk of pregnancy from unprotected sex prior to starting the method, unreliable use of the previous contraceptive method, and/or time needed to establish contraceptive efficacy at the start of the new method.
- Pregnancy tests at start of contraceptive method may not detect an early pregnancy following unprotected sex in the last three weeks.

Any starter on new method contraception should have a repeat pregnancy test at 3 weeks if there is any risk of pregnancy at start of contraceptive method

- The duration of teratogen prescriptions may need to be shortened for patients who use contraceptive methods that require frequent pregnancy testing.

Effectiveness of contraceptive in typical use[1]	Contraceptive method	Duration contraceptive method used / other situations	Pregnancy test needed before next teratogen prescription?
Highly effective methods **(Typical use failure rates less than 1%)**	Copper intrauterine device (copper IUD)	Established user more than 3 weeks to 5-10 years (depending on IUD[2])	No
	Levonorgestrel-releasing intrauterine system (LNG-IUS)	Established user more than 3 weeks to 3-5 years (depending on IUS[2])	No
	Progestogen Implant	Established user more than 3 weeks to 3years	No
		Established user (more than 3 weeks), but concurrent use of interacting medicines which may affect efficacy[3]	Yes + review / refer for contraceptive advice
Effective methods **(Typical use failure rates greater than 1%)** **Additional barrier methods are advised during teratogen use**	Depot medroxyprogesterone acetate (DMPA) subcutaneous (SC) or intramuscular (IM) injections[4]	Established user (more than 3 weeks + repeat injections on schedule) and less than 13 weeks since last injection + documented as administered by healthcare professionals	No
		Established user (more than 3 weeks + repeat injections on schedule and less than 13 weeks since last injection) but self-administered or undocumented administration	Yes, test if any suspected risk of pregnancy
		More than 13 weeks since last injection (i.e. beyond recommended duration of use of last injection)	Yes + review / refer for contraceptive advice
	Combined hormonal contraceptives (pills, patches or vaginal ring) or progestogen-only pills	Established user (more than 3 weeks), reliable and consistent use	Yes, test if any suspected risk of pregnancy
		Established user (more than 3 weeks) but with unreliable or inconsistent use of method, eg: • missed pills, late patch • Diarrhoea or vomiting; • use of other interacting medicines that may affect efficacy[3]	Yes + review / refer for contraceptive advice
	Other methods or no contraception	Any duration of use of other methods	Yes + review / refer for contraceptive advice;
		No contraception	Assess need for contraception + test if any suspected risk of pregnancy + review / refer for contraceptive advice;

Explanatory notes:

1. Effectiveness of methods are based on failure rates in typical use (which includes risk of user error) rather than perfect use. Perfect use failure rates are similar for specific methods listed (0.03 – 0.6%) but risk of user error is higher for daily methods than for long acting reversible contraceptive (LARC) methods and are highest for methods used at time of sexual intercourse. Highly effective methods are based on less than 1% failure rate in typical use; Less effective methods are based on greater than 1% failure rate (6 – 9%) in typical use (Trussell J Contraceptive failure in the United States Contraception. 2011 May;83(5):397-404. doi: 10.1016/j.contraception.2011.01.021. Epub 2011 Mar 12).
2. Refer to Product Information for specific products; patients should be reviewed / referred for contraception advice at the end of the recommended duration of use.
3. Implants are only considered as highly effective and combined hormonal contraceptives and progesterone-only pills are only considered as effective if interactions with any concurrent medicine are not a concern (see FSRH Guidance on Drug Interactions with Hormonal Contraception).
4. DMPA (IM or SC) injection can be considered as highly effective if it is administered by healthcare professionals and continuous repeat use is documented as occurring within recommended duration of action (equivalent to perfect use, failure rate = 0.2%). Otherwise it is considered an effective contraceptive (typical use failure rate =6%). The same rationale should be used for other injection products with different recommended duration of action (e.g. Norethisterone enanthate).

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