الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations II: Pregnant and breastfeeding women

Version 1.0

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Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

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P.II.A. INTRODUCTION

This Product- or Population-Specific Considerations II: Pregnant and breastfeeding women of the Good Pharmacovigilance Practice (GVP) is based mainly on the European guidelines on GVP, and it aims to provide guidance to marketing authorization holders (MAHs)/applicants for facilitating appropriate pharmacovigilance for medicinal products that may be used in pregnant or breastfeeding women.

Guidance on pharmacovigilance for the use of medicinal products in pregnancy and breastfeeding is widely acknowledged as important. Pregnant and breastfeeding women are considered special populations and there may be a potential maternal or embryo/fatal effect. In addition, it is necessary to consider this in the context of women of childbearing potential, as pregnancy may be unplanned or medication used before pregnancy is considered, thus, so the effects of the medicine on pregnancy and the need to avoid pregnancy or for pre-conception counselling may have to be considered by the prescribing physician and the patient in these contexts.

Medicines used during pregnancy specifically aims to benefit the (unborn) child are excluded; 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 considered. 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.

During clinical development of most medicines, pregnant and breastfeeding women are actively excluded from trials, and if pregnancy does occur during a trial, the usual procedure is to discontinue treatment and monitor the women to assess pregnancy outcomes. Consequently, safety data for pregnancy obtained in the pre-authorization phase are limited.

While safety data for pregnancy obtained in the pre-authorization phase are limited, it is important to collect data once a product is placed on the market, especially if use during pregnancy and/or breastfeeding is likely to occur. This helps to obtain a better understanding of the risks associated with such use and to identify and characterize any risks, even if no safety concerns have arisen in the pre-authorization phase. Historically, obtaining data from pregnant

women on medicine use and outcomes during the post-authorization phase has been challenging. However, with the increasing feasibility of accessing data, it is becoming easier to generate knowledge on safety in this population.

Therefore, it is important to have well-documented and adequate data collection and assessment in a timely manner. This will enable patients and prescribers to have relevant information to make informed decisions about using medicine during pregnancy and breastfeeding, and to be well-informed about any uncertainties. Following guidance in this regard will help to minimize adverse outcomes during pregnancy and breastfeeding, without unnecessarily withholding useful treatment options from pregnant and breastfeeding women.

This Product- or Population-Specific Considerations II: Pregnant and breastfeeding women of the Saudi Good Pharmacovigilance Practice (GVP) aims to provide guidance to marketing authorization holders/applicants, and Saudi Food & Drug Authority 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 congenital anomaly/birth defect are (suspected) serious adverse reactions (See GVP-VI.A.1.5 Seriousness). In this GVP Product- or Population-Specific Considerations II, the term 'pregnancy outcome' refers to the result of a pregnancy and hence may be a serious adverse reaction (see P.II.A.2.); this is different from general pharmacovigilance terminology in which the term 'outcome' refers to the result of an adverse reaction.

Considering that the general guidance on pharmacovigilance processes in Saudi Arabia is provided in SFDA-GVP Modules I to XVI, this guidance aims to integrate pharmacovigilance, including risk management and considerations for pregnant and breastfeeding women, with the applicable structures and processes for pharmacovigilance overall.

P.II.A.1 Related guidelines

GVP P.II is intended to be used in conjunction with the Saudi GVP Modules I to XVI and does not replace these modules or introduce additional regulatory requirements beyond those already covered in the existing modules.

The effects of medicines on fertility and the use of medicines in neonates are out of scope of GVP P.II; guidance on these areas is provided in GVP Module V on "RISK MANAGEMENT SYSTEMS".

P.II.A.2. Pharmacovigilance aspects specific to the use of medicinal products in pregnant or breastfeeding women

P.II.A.2.1. Availability and interpretation of data

Pregnant women are often excluded from clinical trials due to ethical concerns, at the time of marketing authorization, 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 authorization 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.

P.II.A.2.2 Adverse events related to physiological changes of pregnancy.

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

Furthermore, for medicinal 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, the availability of specific

data on these phenomena is limited, and generating such data may be difficult when the terms of marketing authorization are such that the product information advises not to use the medicine during pregnancy.

P.II.A.2.3 Susceptible periods and adverse pregnancy outcomes

Susceptibility of adverse pregnancy outcomes from medicine exposure varies at 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 pharmacokinetics half-life). Clinically, gestational age is usually calculated from the last menstrual period, but more accurately established from ultrasound diagnostics. 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. The timing of exposure impact table:

Table 1: Description of the impact of timing of exposure and pregnancy outcomes

Period	Potential pregnancy adverse outcome
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. 148 neural tube defects 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 recognized 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 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-authorization 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.II.A.1.4 Adverse events in the child following exposure through breastfeeding.

P.II.A.2.4. Adverse events in the child following exposure through breastfeeding.

Some medicinal products are excreted in breast milk through breastfeeding, which may have an immediate adverse event on the child (e.g., sedation, irritation, gastrointestinal disturbances). This risk will be higher especially for medicines excreted in breastmilk 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 metabolizing and excreting the medicine. The risk to the child can rely on several factors, 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.

P.II.A.3. Terminology

Terms for defining the foetus at the different stages of the pregnancy	
Terms	Definition
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	
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.
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 localized 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 recognized 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:
Live birth prevalence rate= Number of cases among live born infants /Total number of live born infants *1000	
Birth prevalence rate= Number of cases among live and stillborn infants /Total number of (live + still) born infants *1000	
Total prevalence rate= Number of cases among live births, stillborn and terminated pregnancies /Number of live births, stillbirths and terminated pregnancies *1000	

P.II.B. STRUCTURES AND PROCESSES

P.II.B.1. Risk management plan

Generally, risk management plans (RMPs) will reflect the measures considered necessary to identify, characterize, and minimize a medicinal product's important risks (GVP Module V). These aspects of the RMP should also reflect the available information for the product in relation to pregnancy and breastfeeding. Further, GVP Module V (V.B.5.5) 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.II.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-authorization phase or from products from the same pharmacological class, as well as signals arising in the post-authorization 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 minimization 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-authorization 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 minimization measures (RMM) to be implemented. The RMP also includes the RMM to be implemented and guidance for these is provided in P.II.B.7.

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

Reports, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. When an active substance (or one of its metabolites) has a long half-life, this should be considered when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.

Not infrequently, pregnant women or healthcare professionals will contact MAHs to request information on the teratogenicity of a medicinal product and/or experience of use during pregnancy. Reasonable attempts should be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow-up on the outcome of the pregnancy.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context the use of standard structured questionnaires is recommended.

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported, in accordance with the requirements outlined in VI.B.7.

This especially refers to:

• Reports of congenital anomalies or developmental delay, in the fetus or the child;

• Reports of fetal death and spontaneous abortion; and

• Reports of suspected adverse reactions in the neonate that are classified as serious.

Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which

have a normal outcome, should not be reported since there is no suspected adverse reaction. These reports should however be collected and discussed in the PSUR/PBRERs (See Module VII).

P.II.B.2.1 Content of reports

It is essential that marketing authorization holders collect and provide as many elements as possible for all cases, irrespective of whether or not a product is authorized for use in pregnancy or breastfeeding, to facilitate the evaluation. The initial report should be submitted in ICH E2B message format.

The requirements for the management and reporting of suspected adverse reactions from spontaneous reporting or other sources, 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 VI.B.7 – 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 Module VI.www.sfda.gov.sa) 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 summarized in Table 3 as follows:

Table 2: Requirements for the submission of individual case safety reports with pregnancy exposure

1st situation:	**Adverse reactions reported both in mother and foetus/baby**	
	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)
	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)
	No adverse reaction in child	1 case ‹‹mother››, explicitly stating the pregnancy outcome
2nd situation:	**No adverse reaction in mother and foetus/baby**	
	Spontaneous abortion 1 case	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
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)

P.II.B.2.2 Follow-up of reports

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 complete. If necessary cases with incomplete information should be followed-up to obtain detailed information for comprehensive scientific evaluation of the cases. The reported source should submit additional follow up form include new relevant information. The reported source should not repeat information already provided in the initial report. Appendix 1 lists information that could be collected.

P.II.B.3. Periodic safety update reports (PSURs)

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

- The PSUR needs to include all the relevant safety information related to the exposure during pregnancy and breastfeeding from all available recourses including the spontaneous ICSRs of adverse pregnancy outcomes, or adverse reactions/outcomes in the child following exposure in utero or during breastfeeding. In addition, ICSRs published in the medical literature, ongoing or finalized post-authorization studies (PASS), and ongoing or finalized observational study, e.g. a pregnancy registry, during the reporting interval.
- Age- and sex-specific drug utilization 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 if available. Sources of exposure data may include non-interventional studies, registries, and formal drug utilization 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'

P.II.B.4. Post-authorization safety studies

The requirements for the design and conduct of post-authorization safety studies (PASS) in GVP Module VIII should be followed. 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.II.B.1.) to better characterize potential risk with use of the product in pregnancy and breastfeeding. Marketing authorization holders and SFDA are required to consider whether a PASS would be an appropriate tool for this purpose. A PASS may constitute a drug utilization 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.II.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.

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.II.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 program) (see P.II.B.7.) is needed.
- If adverse events are reported in pregnant women taking a drug
- Changes in dosing or administration of drug in pregnant women
- If a drug is approved for new indication in pregnant women.

If a PASS is considered warranted, it should be designed considering the issue of competing endpoints (see P.II.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.II.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.II.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 utilization studies: descriptive studies to establish the extent of exposure in women childbearing potential, pregnancy and breastfeeding women, as well as utilization/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, considering 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 characterization of associated risks considered necessary) it may be appropriate to initiate a safety study at the time of marketing authorization. In other cases, if a drug utilization 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.II.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.II.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 utilization 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 minimize bias and confounding (see P.II.B.4.2.3.). Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.II.A.1.3.), it is usually

necessary to include participants from more than one country in order to achieve adequate power.

P.II.B.4.2.1. Pregnancy registries

Pregnancy registry actively gathers information on the outcomes associated with exposure to drugs or biological products during pregnancy, which can be used to conduct a prospective observational study (women are enrolled before the pregnancy outcome). 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 authorization holder is complemented with public data sources such as birth defects registries, 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 enroll 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.

P.II.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, pediatric, genetic and neurodevelopmental expertise is crucial.

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

The design and conduct of a PASS in the population of pregnant women should consider the specific characteristics of this population that may lead to confounding. When drug utilization studies are being designed, it is useful to consider including information on such characteristics to aid the design of possible further safety studies. For 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 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 minimize 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.II.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.II.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-authorization 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-born 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.II.B.5. Signal management

Signal management process is a set of activities performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed, based on ICSRs, aggregated data from active surveillance systems or studies, literature information or other data sources (GVP Module IX). Signal management process performed on registered product used in Saudi Arabia. These products include prescription medicines, over-the-counter medicines, complementary medicines, as well as biological products. This section should be followed alongside the general guidance in GVP Module IX on signal management. Pregnancy PV aims to detect signals that might indicate that a particular drug is associated with adverse pregnancy outcomes. Pregnancy-related signals may also include compliance with pregnancy prevention programs and with pregnancy as a labeled contraindication. The signal management process from signal detection to recommendation for action is provided in GVP Module IX.

P.II.B.5.1 Signal detection: Spontaneous reporting

The identification of related cases plays a vital role in supporting signal detection and validation. In order to retrieve all pregnancy outcomes (such as congenital anomalies, spontaneous abortion, stillbirth, and labor complications), the Standardized MedDRA Query (1st level) Pregnancy and neonatal topics' may be useful.

As general PV, an individual clinical assessment of each report is the main strategy for detecting signals in spontaneous pregnancy reports. This method includes checking detailed information (e.g. timing of gestation, duration, and product) regarding exposure during pregnancy, reviewing product information, searching national and global ADR databases for similar reports, and reviewing reference sources and medical literature for previous cases and other relevant information.

P.II.B.5.2 Signal detection: Cohort event monitoring

A cohort event monitoring program may help detect a certain type of signals regarding the prevalence and safety of certain medications during pregnancy.

A comparative cohort study can compare the prevalence of adverse pregnancy outcomes between exposed and unexposed women (with or without the same or similar diseases). Generally, cohort event monitoring uses aggregate data analysis. (Lareb, Pregnancy PV Toolkit).

P.II.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 GCC guidance for Presenting the Labeling Information, SPC and PIL. For communication regarding pregnancy for vaccines, SFDA 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.

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 authorization holders 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;
- Characterization 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;
- 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 program (PPP) and contraception advice (see P.II.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 female patients and their partners, and healthcare professionals (including in particular general practitioners, pediatricians, obstetricians and gynecologists, midwives, nurses and pharmacists).

P.II.B.7. Risk Minimization Measures

In the area of pregnancy and breastfeeding, the objective of risk minimization 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 unintentional 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), considering teratogenic properties and the half-life of the medicinal product (see P.II.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, minimizing exposure via male partners exposed to the medicine by use of barrier contraception and informing the physician if the partner becomes pregnant;
- Minimizing exposure through breast milk by optimized timing of medicine intake, short treatment duration, discontinuation of medication or if minimizing 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.II.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.II.B.7.1. Educational materials

Materials targeted at healthcare professionals and/or women of childbearing potential, pregnant or breastfeeding women may be warranted as part of the RMP (see P.II.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 section P.II.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/care giver);
- 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), or marketing authorization holder;
- Information on the need for pregnancy testing before the start of treatment and, as applicable, during and after treatment.

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 specialties.

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.II.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 (SPC)), women of childbearing potential must be advised, through the patient information leaflet and possibly in addition through educational materials (P.II.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. 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.II.B.7.3. Pregnancy prevention program

When a medicinal product with known teratogenic effect is intended for use in women of childbearing potential, implementing a pregnancy prevention program (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, the following should be taken into account:

- The level of scientific evidence for the teratogenic potential of a medicinal product, including the evidence on the magnitude and nature of the teratogenic effect
- The likelihood of the use of the medicinal product in women of childbearing potential, especially, its potential use under the clinical conditions for which the product is authorized.

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.II.C. OPERATION WITHIN KSA

P.II.C.1. Submission of PSUR in the KSA

For all teratogenic products and for those with pregnancy or breastfeeding related safety concerns in the PSUR, Table 3 below 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 authorization holder.

Table 3 for reporting numbers of individual case safety reports in PSUR

Pregnancy outcome	Prospective reports					Retrospective reports				
	Time of exposure					Time of exposure				
	Before conception	First trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	First trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy										
Spontaneous abortion										
Elective termination (foetal defects) *										
Elective termination (no foetal defects or unknown)										
Stillbirth with foetal defect*										
Live birth with congenital anomaly*										
Live birth without congenital anomaly										
Total										

* the observed phenotype should be specified

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

This questionnaire provides possible parental and neonatal data elements from which relevant points can be selected when establishing a questionnaire of pregnancy exposure to medicinal products.

A. General Information

- Prospective / retrospective case
- Date of initial contact with marketing authorization 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, pediatrician, other)
- Identification of reporter
- Additional identification of the gynecologist-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

Delivery

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

Family history

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

C. Paternal Information If Appropriate

General information

- Age or birth date

Relevant medical history

Medical products exposure

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, hospitalization, 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, hospitalizations, 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. II. Appendix 2: Contraceptive Method & Frequency of Pregnancy testing during treatment with medicine of teratogenic potential

Contraception is categorized as highly effective or effective method based on their failure rates in typical use in the first year. [Footnote 1] 'Typical use' includes user error (for example, missed pills, starting a pack late) or use in circumstances that decrease efficacy such as interactions with concomitant medicines.

Highly effective methods include Copper intrauterine device (copper IUD), Levonorgestrel-Intrauterine delivery system, and Progestogen Implant. The typical-use failure rates are less than 1% and include male or female sterilization.

Effective methods include as following: Progestogen-only injections, which have typical use failure rate of 6%; Combined hormonal contraceptive (pills, patches, or vaginal rings) and progestogen-only pills, which have typical-use failure rates of 9%.

Methods (Natural contraceptive) which used at time of sexual intercourse or based on fertility awareness have higher typical-use failure rates and are not classed as 'effective' for use with medicines with teratogenic potential so should not be relied upon alone.

Pregnancy risk should be assessed prior treatment with medicine of teratogenic potential.

- 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.

The below table provide guidance to prescribers of medicines with teratogenic potential on the frequency of pregnancy testing needed for most common contraceptive method to avoid exposure in pregnancy during treatment, depending on the chosen contraceptive method. It is recommended to print so can be used as a poster in clinics and to update local guidance, as needed. [Footnote 2]

Effectiveness of contraceptive in typical use	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)	No
	Levonorgestrel-Intrauterine delivery system	Established user more than 3 weeks to 3-5 years (depending on IUS)	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	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) intramuscular (IM) injections4	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
	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;

[Footnote 1] Trussell J. Contraceptive failure in the United States. Contraception 2011; 83: 397-404.

[Footnote 2] The Medicines for Women's Health Expert Advisory Group of the Commission on Human Medicines has developed an aide-memoire table to provide guidance to prescribers of medicines with teratogenic potential on the frequency of pregnancy testing needed to avoid exposure in pregnancy during treatment, depending on the chosen contraceptive method.