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Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations III: Pregnant and breastfeeding women and their children exposed in utero or via breastmilk

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P.III.A. Introduction

The evaluation of the benefit-risk balance of the use of medicinal products during pregnancy or breastfeeding and their children exposed in utero or via breastmilk contains additional elements compared with the evaluation for an overall population. In addition to the benefit-risk balance for female patients, beneficial effects and particularly risks for the embryo, fetus, neonate, infant or child must be taken into account. For breastfeeding, both the benefits of breastfeeding and the risks of the medicinal product for the neonate, infant or child exposed through breast milk should be evaluated. Additionally, the effects of the medicinal product on breast milk production and breastfeeding itself should be considered.

Safety data obtained for these evaluations in the pre-authorisation phase are generally limited. In the post-authorisation phase, data collection to better characterise safety is important even where no safety concerns regarding pregnancy or breastfeeding have arisen pre-authorisation.

Based on the assessment of these data, the overall aim is to provide patients and healthcare professionals with information that can support therapeutic decision-making about using medicinal products during pregnancy or breastfeeding.

This Product- and Population-Specific Considerations Chapter P.III of GVP provides guidance to marketing authorisation holders (or applicant where applicable), competent authorities of Member States and the Agency on conducting pharmacovigilance processes for the populations of pregnant or breastfeeding women (or individuals). Medicinal products with an authorised indication in assisted reproduction or obstetrics or pregnancy-related conditions are addressed in this guidance, while medicinal products on fertility are out of scope. Maternal exposure to medicinal products prior to conception, where relevant to pregnancy outcomes, is considered within the scope of this guidance. Paternal exposure to medicinal products is out of scope of this guidance.

This GVP Chapter applies in conjunction with the GVP Modules describing these processes and their Addenda as referenced. In addition, the following documents should be consulted:

- EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling[1];
- SWP/NcWP Recommendations on the Duration of Contraception Following the End of Treatment with a Genotoxic Drug[1];
- PRAC Guideline on Specific Adverse Reaction Follow-up Questionnaires[1];
- ICH-S5(R3) Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals[1]; and
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology - Annex 2 on methods for the evaluation of medicines in pregnancy and breastfeeding[2].

In this GVP Chapter, all applicable legal requirements are referenced as 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". Directive 2001/83/EC as amended is referenced as "DIR", Regulation (EC) No 726/2004 as amended as "REG" and the Commission Implementing Regulation (EU) No 520/2012 as amended as "IR".

[1] www.ema.europa.eu
[2] https://encepp.europa.eu/encepp-toolkit/methodological-guide_EN

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 at the time of marketing authorisation

At the time of marketing authorisation, assessment of potential risks associated with the use of medicinal products in pregnancy usually relies on non-clinical data. Furthermore, knowledge of adverse reactions in the embryo/fetus of other active substances with similar pharmacological properties can provide information, including instances where the mechanism of action of these active substances can lead to embryo/fetal toxicity, thereby suggesting a class effect that requires careful consideration. However, evidence of absence of harm to the embryo/fetus for one active substance cannot be fully extrapolated to other active substances of the same class.

Data on risks for breastfed neonates/infants at the time of marketing authorisation is usually not available. Factors that help assessing safety for breastfed neonates/infants may include but are not limited to pharmacokinetic data (see also P.III.A.1.4.).

P.III.A.1.2. Adverse events related to pregnancy-induced changes in pharmacokinetics and pharmacodynamics

Physiological changes during pregnancy may result in a change in pharmacokinetics and/or pharmacodynamics of the medicinal product in a treated patient. These changes may, in the pregnant female patient, result in reduced treatment efficacy or increased systemic exposure of the active substance leading to toxicity in the mother and/or embryo/fetus; this is particularly important for products with a narrow therapeutic window.

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

Susceptibility to interference from medicinal product exposure resulting in adverse pregnancy outcomes varies at the different stages of embryonic and fetal development, i.e. gestational age. The degree of in utero medicine exposure depends on the pharmacokinetic characteristics such as distribution, including the ability to cross the placenta, and elimination, as well as the treatment regimen including dose and duration.

Clinically, gestational age is calculated from the first day of the last menstrual period (LMP), but more accurately established from ultrasound diagnostics[3]. A full-term pregnancy lasts between 37 completed to less than 42 completed weeks (259 to 293 days) of gestation, while delivery before 37 completed weeks (less than 259 days) is considered preterm. Possible adverse pregnancy outcomes of in utero exposure include pregnancy loss, congenital anomalies/birth defects, fetotoxic effects, premature birth, abnormal labour progression, adverse effects on the neonate, and adverse effects detected during childhood, such as neurodevelopmental disorder (NDD), adult life or manifesting trans-generationally (see P.III.A.2.).

Examples of potential impact of timing of exposure for different pregnancy outcomes are:

- **Gestational week 0-3 + 6 days**: Interference during this period may result in early pregnancy loss;

[3] This refers to the clinical definition of gestational age; embryologists and toxicologists, however, use time from conception.

- **Gestational week 4-11 + 6 days (end of week 4 until end of week 12)**: During this period organogenesis occurs. Adverse interference during this period can lead to major congenital anomalies, noting that each organ has its specific critical period, generally shorter than 8 weeks, or affect brain development that can manifest during childhood
- **Gestational week 12 (+0) to delivery**: During the remaining period of embryo-fetal development, some organ systems remain sensitive to certain interference which may lead to structural anomalies; additionally, there may be impacts on growth or permanent or transient functional birth defects;
- **Late pregnancy or during delivery**: There is the potential for reversible or irreversible physiological impacts on the fetus or neonate. Examples of such effects induced by certain medicines include premature closure of the ductus arteriosus, acute renal insufficiency, pulmonary hypertension, sedation or withdrawal reactions.

It needs to be recognised that if exposure to an active substance mostly results in (early) pregnancy loss, fetal death or stillbirth, then only evaluating the frequency of birth defects would underestimate the embryo-fetal risk. Moreover, when a substance interferes with organogenesis, the initial adverse impact may not only result in structural anomalies but may also disrupt developmental processes in ways that manifest later in gestation or after birth. Perturbations occurring during critical periods of development, throughout pregnancy can lead to functional or neurodevelopmental impairments that may not be apparent at birth but become evident as the child grows. Therefore, adverse outcomes resulting from in utero exposure may not be observed immediately after birth but need longitudinal assessment. This potential temporal disconnect must be considered for study designs, and in the evaluation of developmental risk. Overall, birth defects visible at birth are estimated at 3% of all live births varying depending on the data source, while organ-specific types of birth defects are considerably less frequent, with prevalences in Europe ranging from 0.224 in 10 000 births[4]. If a medicinal product has embryo-fetal toxicity, it is unlikely to lead to an overall increase in the frequency of all birth defects; rather, an increased frequency may be observed in specific types of birth defects associated with the medicinal product's mechanism of action or timing of exposure. Given that exposure to a particular medicinal product during pregnancy is typically limited in the population, the number of resulting adverse pregnancy outcomes will be even smaller, which has implications for data collection and analysis. Additionally, in studies of effects of exposure during pregnancy on the embryo/fetus, a general evaluation of embryo-fetal toxicity should be complemented with presentation of organ specific birth defects, to provide as much information as possible (see P.III.B.4.).

P.III.A.1.4. Adverse reactions in the neonate/infant following exposure through breast milk

Adverse reactions in infants due to exposure to medicinal products through breast milk can occur. For medicines excreted in breastmilk, accumulation may occur in the infant if the quantity taken up is larger than the neonate's/infant's capacity for eliminating the active substance. Pharmacokinetic data relating to the mother and breast milk, together with the bioavailability information or actual exposure data from the neonate/infant, can help estimate the neonate's/infant's exposure through breastfeeding and assess the potential risk. For more information on adverse reactions in neonates and infants, see GVP P.IV..

[4] EUROCAT (2005-2025 and future updates): Prevalence charts and tables | EU RD Platform

P.III.A.2. Terminology

Terms used in this GVP Chapter P.III include:

Embryo: Stage of prenatal development from conception to the end of implantation in the uterus, including organogenesis, through the first ten (10) weeks of gestation computed from the first day of the last menstrual period.

Fetus: Stage of prenatal development from the 11th week of gestational age to birth.

Term and post-term neonate: Offspring from day of birth plus 27 days.

Pre-term - neonate: Offspring from day of birth through the expected date of delivery plus 27 days.

Infant: Offspring from 1 month (28 days) to 23 months of age.

Child: Offspring from 2 to 11 years of age.

Terms specifically defining pregnancy outcomes[5] include:

Miscarriage *(also referred to as "spontaneous abortion")*: Loss of a pregnancy before the fetus reaches viability. This definition is based on gestational age and/or fetal weight and varies across countries and regions. The most recognised definition of miscarriage in the EU is a fetal death that occurs before 20 completed weeks of gestation[6].

Stillbirth: Fetal death after the gestational age of viability. The definition of viability is based on gestational age and/or weight and is variable among countries. The most recognised definition of stillbirth in the EU is a fetal death that occurs after 20 completed weeks of gestation[7].

Termination of pregnancy *(TOP; also referred to as induced abortion and elective abortion):* TOP is a complete expulsion or extraction from a woman of an embryo or a fetus (irrespective of the duration of the pregnancy), following a deliberate interruption of an ongoing pregnancy by medical or surgical means, which is not intended to result in a live birth. Induced abortions are distinct from cases of spontaneous abortion and stillbirth. If a termination of pregnancy is decided in the context of fetal anomaly after prenatal diagnosis, at any gestational age, it is also defined as "termination of pregnancy for fetal anomaly" (TOPFA)[8].

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 e.g. ultrasound. The method used for calculation/estimation should preferably be stated in any report. Gestational age is expressed in completed days or completed weeks.

Pre-term birth *(also referred to as premature birth)**:*** Birth before 37 completed weeks (less than 259 days) of gestation.

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

[5] According to WHO-ICD 11 (WHO "Birth defect surveillance" manual definitions from 2020 and EUROCAT Guide 1.5; national regulations might be different). ICD-11

[6] Given the differences between countries and regions, it is essential to clearly specify the gestational age threshold used in any analysis or report to avoid misclassification and discrepancies in the estimated prevalence of miscarriage across studies and healthcare settings.

[7] Given the differences between countries and regions, the range used in any analysis must always be defined to avoid misunderstanding and discrepancies in the estimated prevalence of stillbirths across different studies and healthcare settings.

[8] Updated definition in line with the definition of WHO-ICD 11. In addition, update of "TOPFA" in line with the EUROCAT definition: TOPFA - Termination of pregnancy for fetal anomaly after prenatal diagnosis, at any gestational age. ICD-11; EUROCAT | European Platform on Rare Disease Registration

Post-term birth: Birth after 42 completed weeks (after 293 days) of gestation.

Low birth weight: Less than 2,500 grams (up to and including 2,499 g) of body weight of the neonate at time of birth.

Very low birth weight: Less than 1,500 grams (up to and including 1,499 g) of body weight of the neonate at time of birth.

Intrauterine growth restriction (IUGR): The fetus does not achieve the expected in-utero growth. It is determined by an estimated fetal weight below the tenth percentile.

Small for gestational age (SGA): The observed weight of a live born neonate or size of a fetus is lower than expected, usually below the tenth percentile, based on gestational age and gender.

Terms specifically defining birth defects include:

Congenital anomaly: A structural or functional anomaly of organs, systems or parts of the body.[9]

Major congenital anomaly: A congenital anomaly that has significant medical, social or cosmetic consequences for the affected individual; this type of anomaly typically requires medical intervention.

Minor congenital anomaly: A congenital anomaly that poses no significant health problem and tends to have limited social or cosmetic consequences for the affected individual.

Teratogen: An agent capable of interrupting or altering the normal development of an embryo or fetus that may result in a congenital anomaly or embryonic or fetal death.

Live birth prevalence of congenital anomalies: Number of live births with congenital anomalies (numerator) among a defined cohort of all live births (denominator).

Birth prevalence of congenital anomalies: Number of live births with congenital anomalies and stillbirths (numerator) among a defined cohort of all live births and (stillbirths) (denominator).

Total prevalence of congenital anomalies: Number of live births with congenital anomalies, stillbirths and elective pregnancy terminations for fetal anomaly (numerator) among a defined cohort of all live births, stillbirths and elective pregnancy terminations (denominator).[10]

P.III.B. Structures and processes

P.III.B.1. Risk management plan

Depending on the available evidence and the authorised indication(s) for the medicinal product, use in pregnancy or breastfeeding may be included in the safety specification of the risk management plan (RMP) as missing information. If safety concerns have been identified in relation to use in pregnancy or

[9] "Congenital anomaly", "congenital abnormality", "birth defect" and "congenital malformation" are often used synonymously to refer to structural birth defects. However, "congenital anomaly" and "congenital abnormality" can also refer more widely to functional (i.e. developmental delay, metabolic disorder, sensory defects, neurodevelopmental disorder (NDD)) and genetic diseases which do not involve structural birth defects, and "congenital malformation" may be used narrowly for errors in morphogenesis excluding disruptions or deformations. "Birth defect" is a more lay-friendly and commonly used term, especially in public health and communication materials. It typically refers to the observable structural anomalies that are present at birth. The term used must always be defined to avoid misunderstanding. In this GVP guidance, "congenital anomaly" will be the preferred term with the above definition. WHO: Birth defects surveillance: A manual for programme managers, 2nd Edition

[10] EUROCAT in its Guide 1.5 Chapter 4 uses a different calculation not including elective terminations in the denominator. The total prevalence as per GVP Chapter P.III definition may be lower than the total prevalence of EUROCAT. It is essential always to describe the calculation used. EUROCAT | European Platform on Rare Disease Registration

breastfeeding and when considering the authorised indication(s), this can be reflected as important identified risk or important potential risk in the safety specification (see GVP Module V).

Based on the overall assessment of available data in relation to in utero exposure during pregnancy or breastfeeding, the need for further post marketing studies, or additional risk minimisation measures (RMM) will be outlined in the RMP (see P.III.B.4. and P.III.B.8.)

P.III.B.1.1. Considerations for follow up data collection on medicinal product exposure of the embryo/fetus during pregnancy

It is good practice to systematically collect information on medicinal product exposure during pregnancy. However, there are specific situations in which assessing embryo-fetal effects following maternal exposure is of particular importance and may be considered in the RMP:

- **Conditions and diseases requiring medicines for a medical need treatment** for maternal and/or embryo-fetal benefit, where discontinuation or omission of treatment would increase risk for both mother and embryo/fetus. In such cases, the potential harm posed by the treatment to the embryo/fetus must be weighed against the risks of untreated disease. Examples include asthma, autoimmune disorders, diabetes mellitus, epilepsy, hypertension, thyroid disorders, infections, intoxications, malignant diseases, severe psychiatric disorders, thromboembolic events as well as the use of general anaesthetics and treatments to prevent transplant rejection. There is a particular need for information when alternative treatment options are limited due to identified or potential risks established from animal studies or human data. Examples include antiepileptics, antineoplastic agents, antithyroid agents and antiretrovirals;
- **Conditions and symptoms commonly treated during pregnancy** even if treatment is not strictly necessary. This includes prescription and non-prescription medicinal products use for common symptoms such as constipation, fatigue, mild to moderate allergic symptoms, common cold, fever, mood alterations, nausea/vomiting and pain. Safety concerns identified in the pre-authorisation phase highlight the importance of collecting exposure data in these situations. Medicinal products for which well-designed epidemiological studies in pregnant women have not demonstrated a risk to the embryo/fetus may, however, be exempted from this close monitoring;
- **Treatment with medicinal products belonging to classes of active substances with structural or mechanistic similarity** to agents known or suspected to have embryo-fetal toxicity in humans based on case reports or animal studies. In such situations, monitoring exposure is of particular importance if pregnancy occurs;
- **Medicinal products representing a new class or a new mode of action** if not already covered by the categories above.

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

Suspected adverse reactions, such as abnormal outcome following parental exposure, including congenital anomalies, potential epigenetic responses, developmental disorders in the fetus or child, fetal death, spontaneous abortion, or adverse reactions in the mother or new-born, are subject to individual case safety reports (ICSR) reporting requirements (see GVP Annex IV, ICH-E2D(R1)). In spontaneous reporting of suspected adverse reactions, all congenital anomaly/birth defects are classified as (suspected) serious adverse reactions (see GVP Annex I). In this GVP Chapter, the term

"pregnancy outcome" refers to the end result of pregnancy, which includes ectopic pregnancy, miscarriage, still birth, termination of pregnancy[11] and live birth (see P.III.A.2.).

The overall requirements for the management of suspected adverse reactions from spontaneous reporting or other sources are described in GVP Module VI.

As ICSRs related to adverse pregnancy outcomes are serious adverse reactions they should be submitted in accordance with the requirements outlined in GVP Module VI.

This especially refers to:

- Reports of congenital anomalies or developmental delay, in the embryo, fetus, neonate, infant or child;
- Reports of still birth and miscarriage; and
- Reports of suspected adverse reactions in the neonate, infant or child that are classified as serious.

In addition, specific handling considerations apply to ICSRs related to the use of a medicinal product during pregnancy or breastfeeding, which are expected to include:

- Timing of exposure (gestational age);
- Coding principles for:
  - Suspected adverse reaction:
    - Comply with the latest version of Guidance for MedDRA Users - MedDRA Term Selection: Points to Consider (see GVP Annex IV);
    - In addition, the MedDRA High-Level Term (HLT "Exposures associated with pregnancy, delivery and lactation" is to be applied for all cases of exposures associated with pregnancy, even if no adverse reactions have been observed as specified in the Guidance for MedDRA Users - MedDRA Term Selection: Points to Consider (see GVP Annex IV)
  - Route of administration:
    - Route of administration for the pregnant woman/mother should be coded as outlined in GVP Module VI;
    - In the case of exposure during breastfeeding, route of administration should be coded as "transmammary" and the MedDRA term "Drug exposure via breast milk" should be used in the Reaction/event ICH-E2B(R3) section (see GVP Annex IV, ICH-E2B(R3))
- Coding of outcomes for exposures during pregnancy must be handled with care to avoid ambiguity. Every effort should be made to obtain and report the actual outcome of the pregnancy, even if this information becomes available only long after the exposure or regardless of whether the exposure was continued or discontinued during pregnancy. When the suspected adverse reaction occurs in the neonate as irreversible congenital anomalies, the outcome option "Not recovered/not resolved/ongoing" should be used (ICH-E2B(R3) data element E.i.7). Depending on the situation, guidance in GVP Module VI should be followed (e.g. if specific adverse reactions occur in the fetus/neonate, a respective case should be created), with coding of the adverse reaction in the

[11] GVP Module VI: "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 submitted as ICSRs since there is no suspected adverse reaction."

reaction section and description in the narrative. This is independent of coding the outcome of the exposure term, which should reflect the latest available information on the exposure;

- In cases where a prevention of congenital anomaly represents the indication for the use of a medicinal product during pregnancy, this information should be captured under the data element for indication (or, where appropriate, in the medical history of the neonate/infant/child);
- Collecting and evaluating information on suspected adverse reactions in the context of off-label use of the medicinal product during pregnancy and breastfeeding.

As many specific information as possible should be collected and included in the structured data elements of the ICSR as well as in the narrative section. The following is of particular value to try to obtain information about:

- The narrative should preferably inform whether the exposure data was collected before (prospective case) or after (retrospective case) the outcome of pregnancy became known. Thus, prospective cases are those that are reported (or recruited if registered into health databases or a study setting) before the conduct of any prenatal tests that could provide knowledge of status of the pregnancy, or before the birth outcome is known, regardless of whether the outcome is adverse or non-adverse. If the condition of the embryo/fetus has already been assessed through prenatal testing at the time of reporting or recruitment, such cases are considered retrospective, irrespective of whether the testing has detected a congenital anomaly or not. For prospective cases, the gestational age at the time of the initial report should be captured. Prospective reports of pregnancy exposure should be actively followed up at key time points by the responsible party that first received the report to ensure comprehensive data collection (see P.III.B.2.1.);
- Gestational age when the suspected adverse reaction was observed in the embryo/fetus and the gestational age at time of exposure should be reported as accurately as possible in the respective ICH-E2B(R3) data element "Gestation period" of the ICSR. Both may be provided in months, weeks, days, or trimester. The method used to assess the gestational age should be specified in the narrative. Information on the exposed medicinal products should be included in the ICH-E2B(R3) section "Drug information" of the ICSR. Information on the exposure to other factors which adversely affect the embryo/fetus (e.g. medication history, 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 data element "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 a medicinal product(s) during pregnancy (see GVP Module VI);
- The results of examinations performed (e.g. fetal ultrasound, amniocentesis, laboratory tests) should be included in the ICH-E2B(R3) section "Results of tests and procedures relevant to the investigation of the patient";
- The modalities for submission of ICSRs are outlined in GVP Module VI as are the specific recommendations for the creation and submission of ICSR of pregnancy exposure (for a summary, see Table P.III.1.).

Table P.III.1.: Submission of individual case safety reports with exposure to a medicinal product during pregnancy

First situation: Adverse reactions reported both in mother and child/fetus[12]	
Miscarriage/Spontaneous abortion	1 case ‹‹mother››
Fetal death without information on malformation	1 case ‹‹mother››
Fetus with birth defects	2 cases: 1 case ‹‹mother›› and 1 case ‹‹fetus›› but cases linked (use data element ICH-E2B(R3) C.1.10)
Congenital anomaly/Birth defects or adverse reaction in neonate/infant/child	2 cases: 1 case ‹‹mother›› and 1 case ‹‹baby››[13] but cases linked (use data element ICH-E2B(R3) C.1.10.r)
No adverse reaction in embryo/fetus/neonate/infant/child	1 case ‹‹mother››, explicitly stating the pregnancy outcome
Second situation: No adverse reaction in mother and adverse reaction in child/fetus	
Miscarriage/Spontaneous abortion	1 case ‹‹mother››
Fetal death without information on malformation	1 case ‹‹mother››
Fetus with birth defects	1 case ‹‹fetus››
Birth defects or suspected adverse reaction in neonate/infant/child	1 case ‹‹baby››[14]
No adverse reaction in child	No case[15]
Specific situation: Multiple births	
	1 case for each birth with a suspected adverse reaction The individual cases should be linked (use data element ICH-E2B(R3) C.1.10.r)

P.III.B.2.1. Follow-up data of reported suspected adverse reactions in pregnancy

The responsible party should make efforts to gather as much follow-up information from initially reported cases of suspected adverse reactions in pregnancy as possible and implement a procedure for this purpose (see also GVP Module VI). A report should contain as much detailed information as possible in order to assess the causal relationships between any reported suspected adverse reaction and the exposure to the suspected medicinal product during pregnancy or in the preconception period. The use of standard structured pregnancy questionnaires is recommended; elements to be considered are provided in GVP Chapter P.III, Appendix 1. When product-specific information is required that is not captured by the standard questionnaire, a specific pregnancy follow-up questionnaire may be considered, in line with the PRAC Guideline on Specific Adverse Reaction Follow-up Questionnaires[16].

The assessment of reports should include evaluation of the suspected reaction observed at the time of birth to identify any congenital anomalies and verify details of maternal exposure. In case of congenital anomalies an assessment of the severity of the anomaly and the final diagnosis should be obtained. In addition, the marketing authorisation holder should make every effort to obtain as much information as

[12] Terminology linked to GVP Module VI
[13] Terminology linked to ICH-E2B(R3) (see GVP Annex IV)
[14] Terminology linked to ICH-E2B(R3) (see GVP Annex IV)
[15] These cases do not meet the definition of an adverse reaction and therefore are not subject to ICSR reporting to EudraVigilance (unless special conditions apply; see GVP Module VI). However, for products not authorised for use in pregnancy, the number of prospectively reported exposures with no suspected adverse reaction in the mother or child and resulting in a healthy neonate should be included in the PSUR under "Exposure during pregnancy", together with relevant data from other sources.
[16] www.ema.europa.eu

possible regarding any further evaluations or conclusions about the outcome from the healthcare system, including any ongoing assessments or follow-up care.

However, in prospective cases[17] that result in a live-born neonate without any congenital anomaly or other adverse outcomes, and herewith are usually not subject of ICSR submission to EudraVigilance, a follow-up concerning the below listed milestones should be conducted in principle only when the medicinal product is associated with pregnancy-related safety concerns identified in the RMP, safety concerns in the periodic safety update report (PSUR) (see GVP Module VII), or if it is based on the assessment of the potential fetal/neonatal effects following exposure of pregnant women to medicinal products in specific situations (see P.III.B.1.1.). In principle, for such medicinal products, cases should be reported to the EudraVigilance database if an adverse reaction is identified during the later stages of follow-up (e.g. at three or twelve months after birth). Of note, in certain circumstances, reports of pregnancy exposure without suspected reactions may still need to be submitted as ICSRs. This may be a condition of the marketing authorisation or stipulated in the RMP, e.g., where use of a medicinal product during pregnancy is contraindicated or where there is a special need for surveillance for a medicinal product because of a high potential for embryo-fetal toxicity (see GVP Module VI).

The following time points are recommended for collection of follow-up information:

- **During pregnancy:** Where relevant (e.g. in prospective pregnancy exposure registries or as per RMP requirements), to obtain missing information on maternal health status, relevant risk factors and details of medicinal product exposure (e.g. gestational age at time of exposure/, dose, duration);
- **At birth:** To assess pregnancy outcomes, including gestational age at time of exposure to the medicinal product(s), birth term, birth weight, presence of congenital anomalies;
- **Three months after delivery:** To collect information on the infant's condition, neonatal or infant complications, potential signs and symptoms of NDD and any follow-up information on congenital anomalies;
- **Twelve months after birth:** In specific cases, to obtain additional information on growth, developmental milestones (e.g. in NDD) and emerging health issues in the infant.

Follow-up beyond these time points may be warranted depending on the nature of the medicinal product, suspected risks and findings during earlier follow-up.

The marketing authorisation holder is not expected to record in their own database exposures during pregnancy or follow up-for products specifically indicated for use during pregnancy (i.e., obstetric medicinal products) if it does not concern a report of a suspected adverse reaction (see also GVP Annex IV, ICH-E2D(R1)).

P.III.B.2.1.1. Pregnancy follow-up questionnaires

Depending on the medicinal product, disease, healthcare setting, and safety concern, additional data elements may be desirable to collect beyond those listed in GVP P.III Appendix 1. In such exceptional cases, the pregnancy questionnaire becomes product-specific and should be included in Annex 4 of the RMP as a specific pregnancy follow-up questionnaire.

[17] Prospective case: pregnancy is known, the pregnancy outcome is not yet known at the time of first reporting of exposure, i.e. reported before the conduct of any prenatal tests that could provide knowledge of the outcome of pregnancy

Follow-up questionnaires (either standard or in exceptional cases specific) (see GVP Module VI and PRAC Guideline on Specific Adverse Reaction Follow-up Questionnaires[18]) are part of the marketing authorisation holder's routine pharmacovigilance processes (see GVP Module V).

Adjudication/case validation of congenital anomaly cases may also be foreseen.

In rare situations, specific follow-up questionnaire for neonates/infants exposed via breastmilk may also be considered (see PRAC Guideline on Specific Adverse Reaction Follow-up Questionnaires[19]).

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

The guidance for periodic safety update reports (PSURs) in GVP Module VII should be followed. Evaluation of data in the PSUR may be one way of further characterising safety of medicine use during pregnancy and breastfeeding. In line with GVP Module VII the following applies:

- Age- and sex-specific exposure data should be included if available (in PSUR section "Estimated exposure and use patterns"), to enhance 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 including formal drug utilisation studies and registries;
- Safety during pregnancy and breastfeeding should be described for medicinal products where pregnancy and/or breastfeeding are included in the PSUR sub-section "Summary of safety concerns" and/or the safety specification of the RMP. However, the same is encouraged also for products where these populations/outcomes are not specified as a safety concern. This information on safety may come from dedicated, non-interventional studies, and in such situations, findings should be presented in PSUR section "Findings from non-interventional studies". For medicinal products for which use during pregnancy or breastfeeding is included in the PSUR section "Summary of safety concerns", spontaneous reports of suspected adverse reactions in embryo/fetus/neonate/infant/child following in utero exposure or in breastfeed infants should be presented in the PSUR section "Signal and risk evaluation". The marketing authorisation holder should also present, in this section an integrated assessment of the interval and cumulative data that has become available. Pregnancy outcomes should be summarised in a table in the PSUR (for the format, see Table P.III.2.);
- For medicinal products for which use during pregnancy or breastfeeding is not listed among safety concerns, spontaneous reports of pregnancy or breastfed infants' outcomes should be presented in the PSUR section "Cumulative and interval summary tabulations from post-marketing data sources";
- Data coming from an ongoing or finalised observational study (see P.III.B.4.) sponsored/conducted by the marketing authorisation holder should be analysed as per the milestones agreed in the RMP. In special situations (e.g. exposure to active substances with identified or potential embryo-fetal toxicity) a report of specific data analysed from the study (not the final study report) may be requested at intervals more frequent than for the PSURs.

[18] www.ema.europa.eu
[19] www.ema.europa.eu

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

For medicinal products for which safety data relating to use in pregnancy and/or breastfeeding are limited, additional pharmacovigilance activities may be warranted (see P.III.B.1.) to better characterise use in these populations and the outcomes. Marketing authorisation holders and competent authorities are required to consider whether a post-authorisation safety study (PASS) would be an appropriate tool for this purpose. PASS should follow the guidance in GVP Module VIII.

Depending on the product characteristics and the context of use, in some situations (e.g. when use in pregnancy is expected and further characterisation of safety in this population is considered necessary) it may be appropriate to initiate a PASS at the time of marketing authorisation. In other situations where a drug utilisation study would show use of the medicinal product in women of childbearing potential or in pregnant women to an extent that studying safety in pregnancy would be warranted, then setting up a PASS for these populations after marketing authorisation might also be considered. Likewise, a safety signal could lead to a request for a study depending on the research question at hand.

The decision whether to request a PASS, and if so, what type of study(ies) (see P.III.A.2.) should be guided by reproductive toxicity studies, signals from spontaneous reports or other data sources, the understanding of the pharmacological class and knowledge regarding the anticipated use pattern.

If a PASS is necessary, it can be carried out using various data sources and study designs, most often using epidemiological methods. (see P.III.B.4.2.1.).

Detailed epidemiological guidance can be found in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[20]; its annex 2 offers specific information on methods for the evaluation of medicinal products used in pregnancy and breastfeeding[21].

The decision to request additional pharmacovigilance activities in the RMP should be taken in a risk-proportionate manner. Considerations regarding risk proportionality differ between the populations of pregnant women and breastfeeding women. Carrying out a PASS may be of particular value in the following situations:

- Where the medicinal product is used to treat conditions that occur commonly in women of childbearing potential;
- When use of the medicinal product cannot be discontinued during pregnancy due to the disease being treated, when a disorder that needs treatment arises during pregnancy, or where changes in treatment during pregnancy would be associated with risks for the pregnant woman and/or the embryo/fetus;
- If a potential risk to the embryo/fetus/neonate/infant/child has been suggested by non-clinical data, a signal (see P.III.B.6.) or based on the chemical or pharmacological properties of the medicine;
- Where strict measures to avoid exposure are implemented, additional studies to further characterise an embryo-fetal risk are often not justified or feasible. In such situations, the evaluation should rather focus on the effectiveness of the RMM; or

[20] ENCePP Methodological Guide - European Union
[21] Annex 2 to the Guide on Methodological Standards in Pharmacoepidemiology - Guidance on methods for the evaluation of medicines in pregnancy and breastfeeding (2nd Edition) (europa.eu)

- If measuring effectiveness of RMM is put in place to avoid exposure during pregnancy due to risk for serious harm to the embryo/fetus/neonate/infant /child (see P.III.B.8.).

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

In cases where a medicinal product is indicated for conditions that necessitate continued treatment during pregnancy (e.g. HIV infection, diabetes, hypertension), and where existing data do not suggest a potential for harm, consideration should be given to conducting pharmacokinetic studies to evaluate the effect of pregnancy on medicinal product exposure. Such study aims to provide information on the need for dose adjustments arising from 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 pregnant woman/mother enhances the likelihood of a healthy child; or products with a relatively narrow therapeutic window.

P.III.B.4.2. Epidemiological studies

Main study types by objective include:

- **Drug utilisation studies (DUS)**: descriptive studies to estimate the extent of exposure in women of childbearing potential, pregnant and/or breastfeeding women, as well as utilisation/ switching/ discontinuation patterns and time trends, as well as description of user characteristics, lifestyle factors, medical conditions etc that could affect embryonic, fetal or neonatal outcomes;
- **Drug safety studies**: Pharmacoepidemiological studies of specific adverse outcomes following exposure to a medicinal product, taking into account the impact of the underlying maternal condition (i.e. non-exposed disease comparison group, active disease comparison or another method to analyse confounding by indication) and other potential confounders;
- **Studies to evaluate the effectiveness or broader impact of RMM**: Drug utilisation studies can also be designed to show changes in use over time e.g. with implementation of RMM measures in specific populations.

P.III.B.4.2.1. Data sources

A number of data sources are available in the EU for carrying out drug utilisation studies and other non-interventional PASS (see P.III.C.2.). Given the usually limited exposure to medicinal products in pregnancy and the low incidence of adverse outcomes (see P.III.A.1.2.), it is usually necessary to include participants from more than one country in order to achieve adequate study size.

Study designs may include registry-based studies that use existing pregnancy or disease registries, or cohort studies with primary data collection. Make a clear distinction between registries and registry-based studies as defined in the EMA Guideline on Registry-Based Studies[22] and use the terminology set out in that guideline. In this context, a study that recruits women specifically for the study and focuses on exposure to a single product should generally be considered a cohort study, whereas a registry-based study uses data from a pregnancy or disease registry that exists independently of the study.

Studies using data sources designed to capture pregnant women with the disease regardless of exposure status are generally more valuable because they allow for a comprehensive, longitudinal

[22] www.ema.europa.eu

examination of treatment and its effects throughout pregnancy. This includes tracking changes in treatments, comparing different therapies and analysing pregnancy outcomes in both exposed and unexposed populations.

The use of existing data sources such as (pregnancy) registries, cohorts or healthcare data sources are primarily recommended to enhance long-term follow-up, facilitate the inclusion of comparator groups, make use of existing infrastructure for data collection and analysis and to avoid unnecessary duplication of effort and enhance efficiency in general.

Studies should be inclusive rather than exclusive by means of comprehensive inclusion criteria in a way that encourages the collection of a diverse and extensive set of data or participants. In settings of primary data collection and cohort studies, retrospective enrolment may introduce bias, but 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 development beyond the neonatal period or infancy. In such cases and if the active substance is present in breastmilk, it is considered useful to additionally include information regarding breastfed neonates/infants, if feasible (for example breastfeeding status (exclusive, partial or none) and information about potential infant's adverse reaction(s)).

It is vital to conduct a feasibility assessment prior to study conduct to evaluate possible data sources and their respective features. Such a feasibility analysis should include estimation of time to recruit a sufficient number of exposed pregnancies within each data source (addressing also differences between different countries of study conduct and external validity of the study). The guidance on feasibility assessment in GVP Module VIII should be followed. In addition, the "Checklist for evaluating the suitability of registries for registry-based studies" in the EMA Guideline on Registry-Based Studies[23] and the ENCePP Checklist for Study Protocols[24] are examples of tools to further guide the conduct of the feasibility assessment.

P.III.B.4.2.2. Study design

The design and conduct of a non-interventional PASS in pregnant women should take into account the specific characteristics of this population that may lead to bias and confounding. Depending on the primary outcomes of interest, it may be necessary to design and conduct multiple studies using a variety of data sources to adequately address different research questions and ensure as comprehensive data sets as possible. Since the timing of exposure may influence the nature and likelihood of adverse pregnancy outcomes, efforts should be made to collect information on adverse outcomes potentially related to exposure to medicinal products throughout all relevant stages of human development, including before conception, during embryo/fetal development (in utero; exposure during a specific trimester), at birth, in the neonatal and infant periods and during breastfeeding, where the neonate or infant may be exposed to the medicinal product through breast milk. For guidance on long-term effects, please see P.III.B.4.2.3..

Factors of importance for interpretation of main pregnancy outcomes should be recorded. Examples include smoking, alcohol intake, folic acid intake, body-mass index (BMI) and other factors relating to fetal or neonatal development (e.g. maternal pregnancy complication, prior history of negative pregnancy outcomes or pre-term birth, prescription of known teratogenic or embryo-fetal toxic

[23] www.ema.europa.eu
[24] https://encepp.europa.eu/

medicines, maternal background disease likely to cause/contribute to embryo/fetal or neonatal adverse consequences). Additionally, the 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/outcomes (e.g. stillbirth, miscarriage, termination of pregnancy (TOP/TOPFA)).

Study design elements that enable less biased results include the use of different comparators, internal 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).

Proposed studies should specifically address and justify:

- Pregnancy exposure windows to be studied;
- Method to determining gestational age;
- Approach to handling challenges with competing endpoints;
- Approach to handling, if applicable, exposures to other medicinal products in the analysis including possible switching patterns between medicinal products (both in planned and unplanned pregnancies);
- Selection of pregnancy outcomes and outcomes in the child for evaluation;
- Selection and justification of the comparator(s) defining the causal contrast (e.g., unexposed, active comparator, or timing-based contrasts) used to interpret the study results.

Further considerations on handling of bias and confounding are available in the GVP Module VIII as well as in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology[25].

P.III.B.4.2.3. Long-term pregnancy outcomes

Evaluating the long-term effects of the use of medicinal product(s) during pregnancy on a child can be challenging, especially as some adverse outcomes may not become apparent until many years after exposure. Generally, the decision as whether 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., anomalies, prematurity, growth retardation, fetal and neonatal outcomes), pharmacological properties, and signals regarding adverse long-term outcomes. When assessing neurodevelopmental outcomes, it is important to consider the varying timelines for the development of motor and language skills, which evolve from basic abilities at birth to more advanced skills later in childhood. Therefore, different measurements should be employed at different developmental stages.

Depending on the specific outcome of interest, follow-up may extend into preschool, school age, and even adolescence, to adequately capture relevant neurodevelopmental outcomes. A complementary approach data from existing registries/databases and studies with primary data collection may be needed.

P.III.B.4.2.4. Clinical breastfeeding studies

When no human data are available regarding the extent of the active substance transfer into breast milk and use among breastfeeding women is anticipated to be common, a pharmacokinetic study in lactating women should be considered, taking into account the pharmacological properties of the medicinal product. Such study should include collection of breast milk samples for measurement of

[25] www.ema.europa.eu

levels of the active substance in breast milk. If feasible, estimation of a relative neonate/infant dose is encouraged to support risk assessment.

Moreover, data on the effect of the medicinal product on milk production or composition may be collected, if potentially clinically relevant.

Where suspicion of serious adverse effects in breastfed neonates/infants arises from pre- or post-authorisation data, breastfeeding is generally not recommended. However, to further characterise such risks, and where feasible, appropriate safety studies using real-world data sources, e.g. medical records, healthcare databases or patient registries (see P.III.B.4.2.1.), may be conducted to evaluate immediate and long-term outcomes in neonates/infants/children previously exposed to the medicinal product via breastfeeding.

P.III.B.5. Other potential sources of information

The sources listed below are intended to support access to additional information relevant to congenital anomalies in the context of pharmacovigilance activities related to pregnancy. This list is not exhaustive and does not imply a requirement for use but highlights key sources at both EU and international level that may assist in the assessment of potential risks.

P.III.B.5.1. European Union-oriented sources

EU-oriented sources include:

- **EUROCAT (JRC-EU Platform)**: European network of population-based registries (more than 36 in 21 countries) covering about 25% of EU births; epidemiological surveillance, prevalence tables, prenatal detection, early warning systems, prevention, research, data management tools[26];
- **European Teratology Information Services (ENTIS)**: Clinical-pharmacological network providing teratogen counselling; cohort studies on medicines exposure and fetal outcomes; core data guidelines for pharmacovigilance[27];
- **Mothers Using Medicines Safely platform (MUMS)** (developed by IMI ConcePTION[28] and ENTIS): Provides teratology information on medication/active substances exposures and associated congenital malformation risks[29]

P.III.B.5.2. International and global sources

International and global sources include:

- **Global Birth Defects Initiative (TGHN)**: Provides a surveillance toolkit for coding/recording externally visible congenital anomalies; supports low-resource settings, training, manuals; aims to strengthen global surveillance[30];
- **International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)**: Global registry network promoting data-driven surveillance and prevention[31];

[26] European Commission, EUROCAT Network; https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-network_en
[27] https://www.entis-org.eu/
[28] www.imi-conception.eu
[29] https://www.mums.eu/
[30] https://globalbirthdefects.tghn.org/
[31] http://www.icbdsr.org/

- **National Birth Defects Prevention Network (NBDPN)**: USA population-based network providing surveillance guidelines, annual reports, data sets, coding and statistical tools and awareness materials[32];
- **Society for Birth Defects Research & Prevention (Teratology Primer)**: Educational content: definitions, epidemiology, genetics, prenatal screening, infection and obesity-related risks, gene–environment interactions[33];
- **WHO-Europe indicator portal**: Offers standardised indicator data on congenital anomalies per 100,000 live births across European countries[34].

P.III.B.6. Signal management

Signal management activities regarding potential adverse pregnancy outcomes and potential adverse outcomes due to exposure via breast milk should be performed in accordance with the guidance provided in GVP Module IX. A signal of a possible teratogenic effect (e.g. a cluster of similar abnormal outcomes) should be notified immediately to the competent authorities, in line with these signal management requirements.

In addition, some of the challenges with signal detection on spontaneously reported suspected adverse reactions in the post-authorisation phase that are specific to the population of pregnant women should be considered. Signal detection in this population remains challenging due to methodological issues, including the baseline incidence of certain anomalies/birth defects, variations in reporting practices, and the complexity of pregnancy-related symptoms, which can be difficult to interpret as they are often confounded by or resemble other conditions.

Pregnancy:

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, miscarriage, stillbirth, risk of labour complications), so that patterns of adverse outcomes may be recognised as signals for further risk assessment. It should be noted that e.g. congenital anomalies are more likely to be detected at birth and thus more likely to be reported in association with exposure in utero. Reactions with a delayed onset or a delayed diagnosis (e.g. those that do not involve visible anomalies, such as NDD) 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 obtain detailed information on exposure during pregnancy, including the timing within gestation, dose and duration of treatment, and the specific medicinal product. This is particularly important to enable assessment of potential associations between in utero exposure and later outcomes, such as NDD diagnosed in the child. Such data can be gathered by identifying cases where relevant details are reported, for example those classified under the seriousness criterion "congenital anomaly/birth defect," cases involving trans-placental exposure, or where gestational age at the earliest exposure is documented.

In the absence of a ICSR pregnancy-specific data element in the electronic format for safety report submissions, the use of the SMQ "Pregnancy and neonatal topics (PNT)" may be overly broad and

[32] https://nbdpn.org/
[33] https://birthdefectsresearch.org/
[34] https://gateway.euro.who.int/.../congenital-anomalies-per-100-000-live-births

suboptimal in certain cases. It is therefore recommended to consider utilising the EMA rule-based algorithm in EudraVigilance (EV) to more efficiently retrieve reported cases of suspected adverse reactions during pregnancy, thereby reducing the burden of manually excluding irrelevant cases. With a positive predictive value (PPV) of 90%, the algorithm significantly outperforms the SMQ PNT, which has a PPV of 54%, supporting its adoption to enhance signal detection activities related to medicine use in pregnancy. The algorithm can be fine-tuned to align with the specific objectives of each organisation. A detailed description of the variables included in the EV pregnancy algorithm is provided in P.III. Appendix 2[35].

Breastfeeding:

For adverse outcomes due to exposure via breast milk, the SMQ (1st level) "Pregnancy and neonatal topics" can be used to retrieve "Lactation related topics (including neonatal exposure through breast milk)" (SMQ) that include "Functional lactation disorders" and "Neonatal exposures via breast milk".

P.III.B.7. Safety communication

The general guidance in GVP Module XV on safety communication and communication-related aspects of GVP Module XVI on risk minimisation measures (RMM) should be followed. In addition to the relevant sections of guidelines referred to in P.III.A., the European Commission Guideline on the Summary of Product Characteristics[36] and the European Commission Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[37] are applicable. For communication regarding pregnancy for vaccines, GVP Chapter P.I. should be followed too.

The specific communication objectives for medicinal products which may be used by women 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, promoting adherence to RMM and supporting informed choices where the wish for a child exists, while addressing the medical needs of the woman. As for breastfeeding women, appropriate safety communication would result in preventing unnecessary temporary or permanent interruption of the mother's medical treatment or breastfeeding disruption.

Communication therefore should be tailored to women (and their partners, or parents /carers in the case of paediatric patients), as well as concerned healthcare professionals, to address their specific information needs.

P.III.B.8. Risk minimisation measures

Information on the risk and actions for risk minimisation are to be included in the product information. Tools of additional RMM may be required, e.g. educational/safety advice materials. In certain circumstances, a set of additional RMM tools may be required to address embryo-fetal risks (see GVP Module XVI and GVP Module XVI Addendum I).

Information regarding the existence of an activity for structured follow-up data collection regarding the use of the medicinal product in pregnancy, such as a PASS, can be included in pregnancy-related additional RMM materials, e.g. educational/safety advice materials (see GVP Module XVI).

[35] Zaccaria C, Piccolo L, Gordillo-Marañón M, et al. Identification of pregnancy adverse drug reactions in pharmacovigilance reporting systems: a novel algorithm developed in EudraVigilance. Drug Saf. 2024: 47:1127-1136
[36] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf

[37] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf

P.III.C. Operation of the EU network

P.III.C.1. Periodic safety update reports in the EU

For all medicinal products with pregnancy-related safety concerns included in the RMP or the PSUR, regardless of the source of information (e.g. spontaneous reports - ICSRs, PASS), a table following the format shown in Table P.III.2. should be provided and completed in full. For all other medicinal products GVP Module VII should be followed. Additionally, any suspected neonatal adverse reactions and congenital anomalies should be presented. Overall anomaly rates as well as the proportional prevalence (distribution of the anomaly and risk factors in populations at a specific pregnancy stage) of individual congenital anomaly have to be compared with relevant reference prevalence rates and discussed, if relevant, by the marketing authorisation holder.

Information presented in the PSUR should be cumulative data to allow for comprehensive assessment of data and observed patterns for pregnancy (and breastfeeding, as applicable) related events. In case the PSUR frequency is not considered adequate (e.g. too long) to allow for timely assessment of pregnancy and/ or breastfeeding related concerns, submission of cumulative data in dedicated procedures is possible to request.

The congenital anomaly 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[38].

Table P.III.2.: Table for reporting numbers of individual case safety reports (ICSRs) in periodic safety update reports (PSURs)

Pregnancy outcome	Prospective cases[39] Number					Retrospective cases[40] 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										
Miscarriage										
Termination of pregnancy for fetal anomaly (TOPFA)[41] (specify major congenital anomaly in brackets)										
Termination of pregnancy (TOP) (no congenital anomaly or unknown)										

[38] The rate is usually compared to external reference data which can give an indication on whether the rate is higher than expected.
[39] Prospective case: pregnancy is known, the pregnancy outcome is not yet known at the time of first reporting of exposure, i.e. reported before the conduct of any prenatal tests that could provide knowledge of the outcome of pregnancy.
[40] Retrospective case: pregnancy outcome is known at the time of first reporting the exposure; if the condition of the fetus has already been assessed through prenatal testing (e.g. targeted ultrasound, amniocentesis), such data are considered retrospective, irrespective of whether the testing has detected a malformation or not.
[41] The observed phenotype should be specified.

Stillbirth with congenital anomaly[41] (specify major congenital anomaly in brackets)										
Stillbirth without congenital anomaly										
Live birth with congenital anomaly[41] (specify major congenital anomaly in brackets)										
Live birth without congenital anomaly										
Unknown										
Total										

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

Several data sources in the EU are available for carrying out post-authorisation safety studies (PASS), including drug utilisation studies, in pregnancy, as compiled by the European Network of Centres for Excellence in Pharmacovigilance and Pharmacoepidemiology (ENCePP) - Guidance on Methods for the Evaluation of Medicines in Pregnancy and Breastfeeding[42]. Additionally, an overview of EU data sources available in principle for the evaluation of long-term pregnancy outcomes, with details on content as well as governance, is available in the HMA-EMA Catalogues of Real-World Data Sources and Studies[43].

Reliable information regarding patient exposure for PASS in breastfeeding is not routinely available but may exist in some birth cohorts in EU Member States.

Study protocols and results should be submitted to the competent authorities in Member States or to EMA, as applicable, and be made available through the above-mentioned Catalogues[44]. The latter is an obligation on marketing authorisation holders for all imposed PASS and encouraged for all other PASS (see GVP Module VIII).

[42] Annex 2 to the Guide on Methodological Standards in Pharmacoepidemiology - Guidance on methods for the evaluation of medicines in pregnancy and breastfeeding (2nd Edition) (europa.eu)
[43] Homepage | HMA-EMA Catalogues of real-world data sources and studies (europa.eu)
[44] Catalogue of RWD studies | HMA-EMA Catalogues of real-world data sources and studies (europa.eu)

P.III. Appendix 1: Questionnaire to collect information on pregnancy exposure (standard pregnancy questionnaire)

This Appendix provides a list of possible parental and neonatal data elements to support the structured collection of relevant information when establishing a standard follow-up questionnaire for pregnancy exposure to medicinal products. While some of these data elements correspond directly to existing ICH-E2B data elements, others may not be explicitly covered but can be captured through narrative information or appropriately mapped to data elements such as medical history and concurrent conditions (ICH-E2B(R3) data element D.10.7), past medicine history (ICH-E2B(R3) data element D.10.8), or test results (ICH-E2B(R3) data elements in section F). The aim is to facilitate the comprehensive collection of pertinent information needed for case evaluation, regardless of whether it is recorded using MedDRA terms or free-text entries. Collection should be tailored to the specific condition, disease or exposure of interest.

A. GENERAL INFORMATION

- Prospective/retrospective case

- Date of initial contact with marketing authorisation holder

- Source of information (as per ICH-E2B(R3) data element "reporter qualification"; 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 delivered

B. MATERNAL INFORMATION

- Identification of the pregnant woman receiving the medicinal product

- Date of birth (or age)

- Weight, height

Obstetrical history:

- Number of previous pregnancies and outcome (e.g. live birth, miscarriage, termination of pregnancy (TOP), termination of pregnancy for fetal anomaly (TOPFA) with specification of gestational length and context, stillbirth, ectopic pregnancy)

- Previous maternal pregnancy complications

- Previous embryo/fetal/neonatal abnormalities and type

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, sexually transmitted disorders, hepatitis, AIDS (specify viral load, CD4 count), and other, including other predisposing factors for neurodevelopmental disorders (NDD).

- History of subfertility

Current pregnancy:

- First day of last menstrual period (LMP)
- Gestational age at the time of the reporter first contact with marketing authorisation holder (specify if based on ultrasound or LMP)
- Gestational age at the time of medicinal product exposure, preferably based on ultrasound and with the method of determining gestational age specified
- Estimated date of delivery
- Number of fetuses
- Treatment for infertility (specify)
- Exposure to medicinal products subject to medical prescription, over the counter (OTC) products, pregnancy supplements such as folic acid, multivitamins:
    - Name
    - Dosage and route
    - Date of first use, date of end of treatment, duration
    - Indication
- Contraceptive method used
- Use of tobacco, alcohol, recreational or illicit drugs (specify amount and if stopped during pregnancy)
- Results of serology tests, e.g. rubella, toxoplasmosis
- Complications during pregnancy and date (including any adverse reactions)
- Disease course(s) during pregnancy and any complications
- Antenatal check-up (specify dates and results, e.g. fetal ultrasound, serum markers), chorionic villi biopsy (CVB), amniocentesis, non-invasive prenatal test

Delivery:

- Date of delivery
- Mode of delivery
- Labour/delivery complications (fetal 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

Medicinal products exposure

D. NEONATAL/INFANT/CHILD INFORMATION

Initial:

- Source of information
- Date of receipt of information
- Outcome of pregnancy and date (stillbirth, live birth)
- Date of birth
- Gestational age at birth
- Sex of neonate
- Results of neonatal physical examination including:
    - Weight at birth
    - Length, head circumference at birth
- Malformation/congenital anomalies diagnosed in a fetus 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
- Withdrawal syndrome
- Neonatal death (date)

Follow-up[45]:

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

E. EMBRYO/FETAL INFORMATION in the case of TOP, TOPFA, miscarriage, and stillbirth

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

[45] At least 3 months after birth and where relevant, 1 year after birth for neonatal development outcomes

P.III. Appendix 2: Description of the variables included in the algorithm developed in EudraVigilance, including the rationale for inclusion and exclusion

From: Zaccaria C, Piccolo L, Gordillo-Marañón M, et al. Identification of pregnancy adverse drug reactions in pharmacovigilance reporting systems: a novel algorithm developed in EudraVigilance. Drug Saf. 2024: 47:1127-1136.

ICH-E2B(R3) data element	**Inclusion/exclusion criteria**	**Rationale**
Patient age D.2.1 D.2.2a D.2.2b	Is aged **<** 50 years	Cut-off age until 50 years aims at improving precision by reducing data quality issues.
Gestation period D.2.2.1a D.2.2.1b G.k.6.a G.k.6.b	Is not null	Including cases where the data element was populated aims at improving sensitivity.
Route of administration G.k.4. r.10.2b	Is equal to: intra-amniotic *OR* transplacental use	Including cases where the data element was populated with "Intra-amniotic" *OR* "Transplacental use" aims at improving sensitivity.
Reported Drug Indication G.k.7. r.2b	Is not equal to MedDRA: HLT "Contraceptive methods female" *OR* HLGT "Menstrual cycle and uterine bleeding disorders" *OR* SMQ "Lactation related topics (incl. neonatal exposure through breast milk)" level 2 (narrow)	Majority of cases reported with these indications describe ineffective contraception. Excluding these cases, unless other conditions are met, improves the precision of the algorithm in line with the case definition.

ICH-E2B(R3) data element	Inclusion/exclusion criteria	Rationale
	Is equal to MedDRA: HLT "Exposure associated with pregnancy, delivery and lactation"	Including cases where the indication is reported as maternal and paternal exposure (while excluding lactation related topics) if no other conditions are met, aims at improving sensitivity.
Reported Reaction E.i.2.1b	Is equal to MedDRA: SMQ "Fetal disorders" level 2 (narrow) *OR* SMQ "Termination of pregnancy" level 2 (narrow) *OR* SMQ "Pregnancy labour and delivery complication and risk factors (exc. abortion and stillbirth)" level 2 (narrow)	These SMQs level 2 are included entirely in the algorithm to maintain high sensitivity on these terms that are highly specific for medicines exposure during pregnancy.
	Is equal to *MedDRA:* SMQ "Congenital and genetic disorders" level 2 (narrow) SMQ "Neonatal disorders" level 2 (narrow) *AND* Parent child report* is equal to "Yes" *OR* Seriousness congenital is equal to "Yes"	This strategy is used to reduce false positive generated by MedDRA multi-axiality and/or data quality issues, improving precision. *A safety report is classified as a Parent Child report if at least one of the D.10. data element fields (i.e. Parent section) is populated.
	Is not equal to MedDRA: SMQ "Lactation related topics" level 2 (narrow) *OR* SMQ "Normal Pregnancy" level 2 (narrow)	Cases associated with lactation can be effectively retrieved using the dedicated SMQ level 2. The precision is improved by reducing cases that describe paediatric exposure rather than in utero exposure. Removing cases from the SMQ 'Normal pregnancy' improves precision, in line with both our case definition and GVP Module VI (i.e. cases with normal or no outcomes described, should not be

ICH-E2B(R3) data element	Inclusion/exclusion criteria	Rationale
	OR HLGT "Menstrual cycle and uterine bleeding disorders" *OR* HLT "Contraceptive methods Female" *OR* PT "No adverse reaction" *OR* PT "Ectopic pregnancy with contraceptive device" *OR* PT "Ectopic pregnancy under hormonal contraception"	reported as an ICSR—except for condition of the marketing authorisation or stipulated in the RMP). Removing MedDRA terms related to lack of efficacy of contraceptive methods aims at improving precision in line with our case definition.

Note: Some of the ICH-E2B(R3) data elements above are not mandatory and therefore may be left blank by the reporter. Reports where such data element fields are not populated will not be picked up by the algorithm, unless they meet any of the other conditions.

Abbreviations: *EV* EudraVigilance, *GVP* Good Pharmacovigilance Practices, *ICSR* Individual Case Safety Report, *SMQ* Standardised MedDRA Query, *HLGT* MedDRA High Level Group Term, *HLT* MedDRA High Level Term, *PT* Preferred Term, *RMP* risk management plan