1 2 February 2026
2 EMA/653036/2019 Track-change version following public consultation (not to be quoted as final)

3 Guideline on good pharmacovigilance practices (GVP)

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

Draft finalised by the Agency in collaboration with Member States	27 November 2019
Draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	29 November 2019
Draft adopted by Executive Director	4 December 2019
Release for public consultation	6 December 2019
End of consultation	28 February 2020
Revised draft agreed by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) and finalised by the Agency in collaboration with Member States	5 January 2026
Revised draft agreed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh)	26 January 2026
Revised agreed by the Head of Human Medicines Division as final under delegated authority by the Executive Director	2 February 2026
Date for coming into effect	9 February 2026

6

This track-change version identifies the majority of changes introduced to the public consultation version of this document as the Agency's response to the comments received from the public consultation. This track-change version is published for transparency purposes and must not be taken or quoted as the final version.

* For this reason, the timetable above, and in particular the date of coming into effect, apply only the clean version published as final.

For the final version of this module and any future updates, please see the GVP webpage of the Agency's website.

7

Table of contents

Table of contents

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

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

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

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

~~76~~ ~~This Product- and Population- Specific Considerations Chapter P.III of the Good Pharmacovigilance~~

~~77~~ ~~Practices (~~GVP~~)~~ ~~aims to provide~~ provides guidance to marketing authorisation ~~applicants/~~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).~~for facilitating appropriate pharmacovigilance formedicinal products that may be used in pregnant or breastfeeding women.~~

~~78~~ 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.~~In spontaneous reporting, the term 'adverse event' is synonym to (suspected) adverse reaction and all~~

~~79~~ ~~birth defects are (suspected) 'serious adverse reactions' (see GVP Annex I). In this GVP P.III., the term~~

~~80~~ ~~'pregnancy outcome' refers to the result of a pregnancy and hence may be a serious adverse reaction~~

~~81~~ ~~(see P.III.A.2.); this is different from general pharmacovigilance terminology in which the term~~

~~82~~ ~~'outcome' refers to the result of an adverse reaction.~~

43 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:

44 EMA Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling.

45 SWP/NcWP Recommendations on the Duration of Contraception Following the End of Treatment with a Genotoxic Drug[1].

46 PRAC Guideline on Specific Adverse Reaction Follow-up Questionnaires[1].

47 ICH-S5(R3) Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals[1]; and

48 ENCePP Guide on Methodological Standards in Pharmacoepidemiology - Annex 2 on methods for the evaluation of medicines in pregnancy and breastfeeding .

49 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".

~~83~~ ~~Taking into account that the general guidance on pharmacovigilance processes in the European Union~~

~~84~~ ~~(EU) is provided in GVP Modules I to XVI, the guidance in this GVP P.III aims at integrating~~

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

~~In addition, the following guidelines should be consulted:~~

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

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

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

~~150~~51 *P.III.A.1. Pharmacovigilance aspects specific to the use of medicinal products in pregnant or breastfeeding women*

52 P.III.A.1.1. Availability and interpretation of data at the time of marketing authorisation

~~103~~

~~153~~

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.~~Because pregnant women are rarely included in clinical trials, at the time of marketing authorisation,~~

~~assessment of potential risks associated with the use of medicinal products in pregnancy usually relies on the extrapolation from non-clinical data and on knowledge of adverse embryo/foetal reactions of other products with similar pharmacological properties. There are many examples where the mechanism of action of the medicine is related to the mechanism of teratogenicity or adverse embryo/foetal reaction, and hence pharmacological-toxicological class effects have been observed. Consequently, when assessing potential risks for an active substance, known adverse pregnancy outcomes for another substance of the same class of medicinal products should be carefully considered. However, evidence of absence of harm to the child for one substance cannot be extrapolated to other substances of the same class and be interpreted as indicating the absence of a potential risk for these other substances. Exposure through semen is another route of exposure to the embryo or foetus. Whether this carries a risk in clinical practice is unknown at present, but this should ~~154~~ be considered for highly teratogenic substances that are transmitted into semen.~~

~~Data on risks for breastfed neonates/infants at the time of marketing authorisation is usually not available. Factors that help assess safety for breastfed neonates/infants may include but are not limited to pharmacokinetic data (see also P.III.A.1.4.). ~~Like pregnant women, breastfeeding women are usually excluded from clinical trials; therefore the~~

~~estimation of risks for breastfed infants at the time of marketing authorisation may be based on pharmacokinetic (PK) data, on data about the severity of potential adverse reactions to the medicine in the user population, or data from experience with other products with similar pharmacological properties.~~

[1] ~~www.ema.europa.eu~~

[2] ~~www.ema.europa.eu~~

[3] ~~https://www.ich.org/filcadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5/S5-R3EWG_Step2_Guideline_2017_0705.pdf~~

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

~~physiological changes of pregnancy~~

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.

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

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

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

Susceptibility to interference from medicine exposure resulting in adverse pregnancy outcomes varies at the different stages of embryonic and foetal development~~.~~, i.e. gestational age. The impact 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.

~~ability of a medicine to cross the placenta, dose and duration of such exposure as well as the gestational age at which the exposure occurs (taking into account a product's PK half-life).~~

Clinically, gestational age is usually calculated from the last menstrual period (LMP), but more accurately established from ultrasound diagnostics[4]

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.).

~~. Possible negative consequences of exposure include early pregnancy loss, births defects (teratogenicity), foetotoxic effects, adverse events on the neonate and delayed adverse events on the developing child (see P.III.A.2.). The timing of exposure impacts as follows:~~

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;

~~Gestational week 0-4: interference in the first two weeks after conception may result in early pregnancy loss;~~

- **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 4-16: organogenesis occurs and can therefore be interfered with, resulting in major birth defects. However, each congenital abnormality has its specific critical period, e.g. neural tube defect between the gestational days 29 and 42 (i.e. between days 15 and 28 post-conception);~~

- **Gestational week 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;

~~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 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.

~~Late pregnancy or during delivery: there is the potential for irreversible or reversible physiological impacts on the neonate. These particularly include premature closure of the ductus arteriosus, acute renal insufficiency or withdrawal reactions;~~

~~• Throughout pregnancy: interference through exposure to environmental agents, including medicines, may result in pregnancy loss or stillbirth.~~

It needs to be recognised that if 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[1]. 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 (P.III.B.4.).

~~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~~

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

~~developmental impact later in pregnancy and the perturbed development *in utero* may have~~

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

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

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

~~180~~74 P.III.A.1.4. Adverse events in the ~~child~~ neonate/infant following exposure through ~~breast milk~~breast milk

75 Adverse events
76 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.

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

~~192~~77 *P.III.A.2. Terminology*

~~Terms used in this GVP P.III include: Terms for defining the foetus at the different stages of the pregnancy are:~~

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

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

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

~~203~~78 ~~prenatal development from the conception until the birth.~~ 205

~~Terms for defining pregnancy outcomes[5] are:~~

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

Preterm newborn 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 include:

~~***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: *(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[2].~~Spontaneous abortion and molar pregnancy.~~

~~214~~212***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 recognized definition of stillbirth in the EU is a fetal death that occurs after 20 completed weeks of gestation .

~~***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)[3].(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 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.~~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:

[2] 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.

[3] 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

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

~~(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~~ (293~~4~~ days ~~or more~~) of gestation.

Low birth weight: ~~Body weight of the newborn at birth of l~~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: ~~Body weight of the newborn at birth of l~~Less than 1,500 grams (up to and including 1,499 g) of body weight of the neonate at time of birth.

***Intrauterine growth retardation (IUGR)**:* ~~('small for gestational age'):~~ The fetus does not achieve the expected in-utero growth. It is determined by an estimated fetal weight below the tenth percentile~~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~~.

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:

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

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

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

~~Terms for defining congenital anomalies (birth defects) are:~~

Congenital anomaly: A structural or functional anomaly of organs, systems or parts of the body.[4] ~~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.~~

Major ~~Congenital~~ congenital malformation: A congenital anomaly that has significant medical, social or cosmetic consequences for the affected individual; this type of anomaly typically requires medical intervention. ~~A morphological defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process.~~

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.

~~***Isolated congenital abnormality***: A single localised error of morphogenesis.~~

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

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

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

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

Live birth ~~P~~prevalence of congenital anomlaies: Number of live births with congenital anomalies (numerator) among a defined cohort of all live births (denominator). ~~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 *1000~~

~~Total number of live born infants~~

[4] "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~~

~~***ce rate=*** Number of cases among live and stillborn infants *1000~~

~~Total number of (live + still) born infants~~

~~***Birth prevalence rate=*** Number of cases among live births, stillborn and terminated pregnancies *1000~~

~~Number of live births, stillbirths and terminated pregnancies~~

Birth prevalence of congenital anomalies: Number of life 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).[5]

P.III.B. Structures and processes

P.III.B.1. Risk management plan

277

278 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 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).~~

~~278 for the product in the areas of pregnancy and breastfeeding, the~~
~~279 risk management plans (RMPs) will reflect the measures considered necessary to identify, characterise~~
~~280 and minimise a medicinal product's important risks, as described in GVP Module V. Further, GVP~~
~~281 Module V states that "if the product is expected to be used in populations not studied and if there is a~~

[5] 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 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~~

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

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

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

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

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

P.III.B.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 require 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.

283 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.

284 Medicinal products represent a new class or a new mode of action if not already covered by the categories above.

285

~~313~~286 *P.III.B.2. Management and reporting of suspected adverse reactions*

~~314~~ 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 and live birth (P.III.A.2.). ~~Spontaneous reporting during the post-authorisation phase is one primary source of information on~~

~~315 adverse reactions occurring following exposure *in utero* or during breastfeeding. Reports where the~~

~~316 embryo or foetus may have been exposed to (a) medicinal product(s) (either through maternal~~

~~317 exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in~~

~~318 order to collect information on the outcome of the pregnancy and the development of the child after~~

~~319 birth.~~

~~320~~ The overall requirements for the management of suspected adverse reactions from spontaneous reporting or other sources are described in GVP Module VI.~~It is essential that marketing authorisation holders and competent authorities in Member States collect~~

~~321 and provide as many elements as possible for all cases, irrespective of whether or not a product is~~

~~322 authorised for use in pregnancy or breastfeeding, to facilitate the evaluation. Appendix 1 of this GVP~~

~~323 P.III lists information that could be collected; elements in this Appendix that are not captured in the~~

~~324 ICH-E2B message format (see GVP Annex IV) of the individual case safety report (ICSR), if available,~~

~~325 should be provided in the case narrative.~~

~~326~~ 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. ~~The requirements for the management and~~

~~327 reporting or other sources are described in GVP Module VI, including specific, detailed guidance~~

~~328 regarding the way of ICSR reporting, such as for the items listed below:~~

287 This especially refers to:

288 • Reports of congenital anomalies or developmental delay, in the embryo, fetus, neonate, infant or child;

289 • Reports of still birth and miscarriage; and

290 • Reports of suspected adverse reactions in the neonate, infant or child that are classified as serious.

291 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:

292 • ~~Codin~~ Timing of exposure (gestational age);

~~329~~293 ~~g of reports of use a medicinal product during pregnancy or breastfeeding as follows:~~

~~330 – for the suspected adverse reaction, comply with the latest version of guidance for MedDRA~~

~~331 Users, MedDRA Term Selection: Points to Consider (see GVP Annex IV – MedDRA support~~

~~332 documentation);~~

~~333 for the route of administration, code, in the case of exposure in pregnancy leading to~~

~~334 pregnancy loss or other adverse pregnancy outcomes, the route of administration as~~

~~335 'transplacental' and use the MedDRA term 'exposure in utero' in the Reaction/event section;~~

~~336 and in the case of exposure during breastfeeding, code the route of administration as~~

~~337 'transmammary' and use the MedDRA term 'Drug exposure via breast milk' in the~~

~~338 Reaction/event section. The route of administration for the mother should be coded in the data~~

~~339~~294 ~~elements, parent section of the parent-child report;~~

~~340~~ • Coding principles for:~~outcomes of exposure during pregnancy is open to ambiguity as a record of 'exposure~~

~~341 during pregnancy, resolved' may mean that there is a prospective report of pregnancy exposure~~

~~342 and either exposure discontinued, or the pregnancy has ended. Without reporting any further~~

~~343 information regarding the pregnancy outcome this is not helpful. Efforts must be made to report~~

~~344 the pregnancy outcome, even if this is not known until long after the exposure occurred and~~

~~345 irrespective of whether or not the exposure was discontinued during the pregnancy;~~

295 - 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 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<bullet text>.

~~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;~~

• 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.

~~Collecting and assessing information on off-label use and potential harm.~~

As many specific data elements as ~~are~~ possible ~~to be obtained~~ should be collected and included in the structured data elements of the ICSR ~~(see GVP Annex IV)~~ as well as in the narrative section.

The following is of particular value to try to obtain information about:

~~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 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.);

~~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.~~

~~363~~306 • Gestational age when the suspected adverse reaction was observed in the embryo/~~f~~etus and the
~~364~~307 gestational age at time of exposure ~~need to~~should be reported as accurately as possible in the respective ICH-E2B(R3) data element "Gestation period" of the ICSR.~~.~~ Both may be
~~365~~308 provided in months, weeks, days or trimester. Gestational age should be preferably calculated from
~~366~~309 early foetal ultrasound. The method used to assess gestational age should be specified in the
~~367~~310 narrative. Information on the exposure to any medicinal product should be included in the ICH-E2B (R3)
~~368~~311 section 'Drug information' of the ICSR. Information on the exposure to other factors which adversely affect the embryo/fetus ~~to other teratogens~~ (e.g.
~~369~~312 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 a medicinal product(s) during pregnancy(see GVP Module VI);

- The results of examinations performed (e.g. foetal 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

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

First situation: Adverse reactions reported both in mother and child/fetus[6]	
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)

[6] Terminology linked to GVP Module VI

First situation: Adverse reactions reported both in mother and child/fetus[6]	
Congenital anomaly/Birth defects or adverse reaction in neonate/infant/child	2 cases: 1 case <<mother>> and 1 case <<baby>>[7] 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[11]	
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>>[8]
No adverse reaction in child	No case[9]
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 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[10]).

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 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[11] 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:

[7] Terminology linked to ICH-E2B(R3) (see GVP Annex IV)
[8] Terminology linked to ICH-E2B(R3) (see GVP Annex IV)
[9] 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.
[10] www.ema.europa.eu
[11] 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~~

- **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.

Follow-up questionnaires (either standard or in exceptional cases specific) (see GVP Module VI and PRAC Guideline on Specific Adverse Reaction Follow-up Questionnaires[12]) 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[13].

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

The ~~requirements~~ guidance for periodic safety update reports (PSURs) ~~are detailed~~ in GVP Module VII should be followed. ~~The~~

E~~e~~valuation of data in the PSUR may be one way of further ~~characterising~~characterizing ~~risks~~ safety of medicine use during pregnancy and breastfeeding. ~~In addition, I~~in line with the guidance in GVP Module VII the following applies:

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

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

[12] www.ema.europa.eu

[13] www.ema.europa.eu

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

• Age- and sex-specific 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;

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

~~•~~ Safety during pregnancy and breastfeeding should also be described for products where adverse pregnancy ~~outcomes~~ and/or ~~adverse events associated with~~ breastfeeding are included ~~is a~~in the safety ~~concern~~specification ~~(important risk or missing information) specified in~~of the PSUR and/or the RMP.~~, but it is encouraged also for products where these outcomes/events are not specified as a safety concern~~.

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.);

~~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'.~~

• 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.

~~e.g. a pregnancy registry, should be analysed as per the milestones agreed in the RMP and the analyses should be discussed in the PSUR, as detailed in the guidance on registries in section 5.2.3 of the CHMP Guideline on the~~

~~Exposure to Medicinal Products During Pregnancy: Need for Post-authorisation Data~~

~~(EMEA/CHMP/313666/2005)[8].~~

~~409~~395 *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.~~ ~~The requirements for the design and conduct of post-authorisation safety studies (PASS) in GVP~~

~~Module VIII should be followed, as well as the CHMP Guideline on the Exposure to Medicinal Products~~

~~During Pregnancy: Need for Post-authorisation Data (EMEA/CHMP/313666/2005)[9]. For medicines~~

~~where safety data relating to use of a medicine in pregnancy and breastfeeding are limited, additional~~

~~pharmacovigilance activities may be warranted (see P.III.B.1.) to better characterise potential risk with~~

~~use of the product in pregnancy and breastfeeding. Marketing authorisation holders and competent~~

~~authorities are required to consider whether a PASS would be an appropriate tool for this purpose. A~~

~~PASS may constitute a drug utilisation study or it may investigate specific risks to the embryo, foetus~~

~~or child. Potential study designs for the latter include all epidemiological designs in principle, including~~

~~but not limited to pregnancy registries (see P.III.B.4.2.1.).~~

~~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.~~ ~~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~~

~~426~~396 ~~straightforward~~.

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

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 . Its annex 2 offers specific information on methods for the evaluation of medicinal products used in pregnancy and breastfeeding .

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:~~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:~~

- Where the medicinal product is used to treat conditions that occur commonly in women of childbearing potential;

~~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;~~

- 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 child has been suggested by non-clinical data, a signal (see P.III.B.5.) or based on the chemical or pharmacological properties of the medicine;~~

- 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 the medicine is used to treat conditions that occur commonly in women of child-bearing potential; or~~

- 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

~~if measuring compliance with RMM in place regarding pregnancy or breastfeeding (e.g. in the product information, educational material or a pregnancy prevention programme) (see P.III.B.7.) is needed.~~

- If measuring effectiveness of RMM 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.).

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

~~Possible ethical and feasibility aspects specific to the use of medicines in pregnancy or breastfeeding should be adequately anticipated and managed in the study protocol. Inclusion of pregnant women in a~~

~~PASS should be solely subject to the clinical decision to treat the woman for her medical condition.~~

~~449~~405 P.III.B.4.1. Pharmacokinetic studies on pregnancy-related physiological ~~450~~406 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.

~~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.~~

~~461~~408 P.III.B.4.2. Epidemiological studies

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

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

~~conditions that could lead to adverse embryogenic, foetal or neonatal outcomes, and exposure to~~

~~known teratogenic or foetotoxic medicines;~~

- **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<bullet text>;

~~medicines safety studies: pharmacoepidemiological studies of adverse events of special interest in~~

~~causal association with a medicine, taking into account the impact of the underlying maternal~~

~~condition (i.e. non-exposed disease comparison group) and other potential confounders;~~

- **Studies to evaluate the effectiveness 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.

~~4~~412 ~~Studies to evaluate the effectiveness and broader impact of RMM.~~

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

~~Preferably and if feasible, epidemiological studies should be carried out using existing data sources (i.e. secondary data use) and be designed in such a way as to minimise bias and confounding (see P.III.B.4.2.3.). Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.III.A.1.3.), it is usually necessary to include participants ~~4~~413 ~~from more than one country in order to achieve adequate power.~~

~~4~~414 ***P.III.B.4.2.1. ~~Pregnancy registries~~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 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 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 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 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 and the ENCePP Checklist for Study Protocols are examples of tools to further guide the conduct of the feasibility assessment.~~If additional pharmacovigilance activities in the form of data collection from a pregnancy registry are~~

~~justified, the following should be considered:~~

~~• Registries that, in principle, aim to capture all pregnant women with the disease are generally more useful than medicinal product-specific registries because they provide for longitudinal study of treatment and effects (including switches between products) throughout pregnancy, comparison between products and pregnancy outcomes in an unexposed population;~~

~~• In exceptional cases, a medicinal product-specific pregnancy registry may be appropriate;~~

~~• The use of existing (pregnancy) registries or databases should be considered to enhance long-term follow-up, facilitate the inclusion of comparator groups, make use of existing infrastructure for data collection and analysis, to avoid unnecessary duplication of effort and enhance efficiency in general;~~

~~• It may therefore be prudent to opt for a hybrid study design in which the product-specific information required from the marketing authorisation holder is complemented with public data sources such as birth defects registries, data captured by the teratology information services, or data captured in electronic health records. Useful information may be acquired and study feasibility may be enhanced by combining existing data sources with de novo data collection regarding use of a specific medicinal product in pregnancy;~~

~~• Registries should be inclusive rather than exclusive by means of comprehensive inclusion criteria. Although retrospective enrolment may introduce bias, information entry after the pregnancy outcome is known can still be valuable. Therefore, although prospective enrolment is preferred and should be encouraged, women who wish to enrol retrospectively should not be discouraged to do so and their pregnancy outcomes should be included in the study report. The retrospective nature of such data needs to be accounted for in the analysis;~~

~~• Follow-up may include longer-term evaluation of neonates or infants for developmental maturation. In such cases and if the active substance is present in breastmilk, it is considered useful to additionally include information regarding breastfed infants. The healthcare professionals who fill data in the registry should be encouraged to record whether the mother starts to breastfeed and if so, to ask the mother regarding possible adverse reactions in her infant at each visit;~~

~~• Information regarding the existence of a pregnancy follow-up activity should be included in any mandated pregnancy-related educational materials.~~

~~• The guidance for data collection on pregnancy exposure and outcomes in P.III Appendix 1 should be followed.~~

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

~~527~~421 *P.III.B.4.2.2. ~~Long-term pregnancy outcomes~~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 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 exposures 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[14].

~~528 Assessing the long-term impact of medicine use in pregnancy on the child is challenging, especially as~~
~~529 some adverse health outcomes may not become apparent until many years after exposure. Generally,~~
~~530 the decision as to whether or not to conduct studies into childhood needs to be based on biological~~
~~531 plausibility and/or a combination of information from non-clinical data, clinical data (e.g.~~
~~532 malformations, prematurity, growth retardation, foetal and neonatal outcomes), pharmacological~~
~~533 properties, and signals regarding adverse long-term outcomes. For evaluating neurodevelopmental~~
~~534 outcomes, the time required to develop motor and language skills (from rudimentary skills just after~~
~~535 birth to fine motor or language skills later in childhood) mean that different measurements should be~~
~~536 used at different ages.~~

~~537 Depending on the outcome of interest, follow-up may be into preschool or school age, and/or~~
~~538 adolescence, as appropriate to reflect the neurodevelopmental outcomes mentioned. A complementary~~
~~539 approach combining data from existing registries/databases and studies with primary data collection~~
~~540 may be needed. A multidisciplinary approach involving epidemiological, paediatric, genetic and~~
~~541~~422 ~~neurodevelopmental expertise is crucial~~.

~~542~~423 ***P.III.B.4.2.3. ~~Handling of bias and confounding~~Long-term pregnancy outcomes***

424 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.

425 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.

~~543 The design and conduct of a PASS in the population of pregnant women should take into account the~~
~~544 specific characteristics of this population that may lead to confounding. When drug utilisation studies~~
~~545 are being designed, it is useful to consider including information on such characteristics to aid the~~
~~546 design of possible further safety studies; examples of potential factors of interest include lifestyle~~
~~547 factors (e.g. smoking, alcohol intake, folic acid intake, body mass index (BMI)) or other factors relating~~
~~548 to foetal or neonatal development (e.g. maternal pregnancy complication, prior history of negative~~
~~549 pregnancy outcomes or pre-term birth, prescription of known teratogenic or foetotoxic medicines,~~
~~550 maternal disease likely to cause foetal or neonatal adverse consequences). Additionally, study design~~

~~10 www.ema.europa.eu.~~

[14] www.ema.europa.eu

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

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

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

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

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

P.III.B.4.2.4. 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 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.4.3. Clinical lactation studies~~

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

~~of the medicinal product by lactating women.~~

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

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

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

P.III.B.5. 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[15];
- **European Teratology Information Services (ENTIS)**: Clinical-pharmacological network providing teratogen counselling; cohort studies on medicines exposure and fetal outcomes; core data guidelines for pharmacovigilance[16];
- **Mothers Using Medicines Safely platform (MUMS)** (developed by IMI ConcePTION[17] and ENTIS): Provides teratology information on medication/active substances exposures and associated congenital malformation risks[18]<bullet text>; and

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[19];
- **International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)**: Global registry network promoting data-driven surveillance and prevention[20];
- **National Birth Defects Prevention Network (NBDPN)**: USA population-based network providing surveillance guidelines, annual reports, data sets, coding and statistical tools and awareness materials[21];
- **Society for Birth Defects Research & Prevention (Teratology Primer)**: Educational content: definitions, epidemiology, genetics, prenatal screening, infection and obesity-related risks, gene–environment interactions[22];
- **WHO-Europe indicator portal**: Offers standardised indicator data on congenital anomalies per 100,000 live births across European countries[23].

[15] European Commission, EUROCAT Network; https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-network_en
[16] https://www.entis-org.eu/
[17] www.imi-conception.eu
[18] https://www.mums.eu/
[19] https://globalbirthdefects.tghn.org/
[20] http://www.icbdsr.org/
[21] https://nbdpn.org/
[22] https://birthdefectsresearch.org/
[23] https://gateway.euro.who.int/.../congenital-anomalies-per-100-000-live-births

~~594~~442 *P.III.B.~~6~~5. Signal management*

443 Signal management activities ~~of~~ regarding potential adverse pregnancy outcomes
444 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.

~~595 should be done in accordance with GVP~~
~~596~~445 ~~Module IX.~~ In addition, some of the challenges with signal detection on spontaneously reported suspected
~~597~~446 adverse reactions in the post-authorisation phase that are specific to the population of pregnant
447 women should be ~~taken into account~~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.

448 ~~The identificati~~Pregnancy:

449 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.

450 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.

451 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 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[24].

452 Breastfeeding:

453 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".

~~598 on of relevant cases plays an important role in supporting detection and validation of~~
~~599 signals and consideration should be given to the types of adverse pregnancy outcomes searched for by~~
~~600 designing an appropriate MedDRA search strategy. The Standardised MeddRA Query (SMQ) (1st level)~~

[24] 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

~~601 'Pregnancy and neonatal topics' may be useful to retrieve all pregnancy outcomes (such as congenital~~
~~602 anomalies, spontaneous abortion, stillbirth, risk of labour complications), so that patterns of adverse~~
~~603 outcomes may be recognised as signals for further risk assessment. It should be noted however that~~
~~604 some outcomes, e.g. congenital malformations, are more likely to be detectable at birth and thus more~~
~~605 likely to be reported in association with exposure *in utero*. Reactions with a delayed onset or a delayed~~
~~606 diagnosis (for example those that do not involve visible anomalies, such as neurodevelopmental~~
~~607 adverse effects) may be less likely to be reported in association with exposure in pregnancy.~~

~~608 In this phase of signal detection and verification, efforts should be made to confirm detailed~~
~~609 information (e.g. timing of gestation, duration, product) regarding exposure during pregnancy. This~~
~~610 can be done by identifying cases with the relevant information provided in the case reports (e.g.~~
~~611 seriousness criterion 'congenital anomaly/birth defect', trans-placental route of administration,~~
~~612 gestational age at time of earliest exposure) whenever available. In some situations, spontaneous~~
~~613 reporting of suspected adverse reactions / pregnancy outcomes has helped to confirm suspicions of~~
~~614 embryofoetal toxicity arising from non-clinical studies.~~

~~615~~454 *P.III.B.76. Safety communication*

455 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[25] and the European Commission Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[26] are applicable. For communication regarding pregnancy for vaccines, GVP Chapter P.I. should be followed too.

456 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.

457 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.

~~616 The general guidance in GVP Module XV on safety communication and communication-related aspects~~
~~617 of GVP Module XVI on RMM should be followed, together with the considerations in this Section. In~~
~~618 addition to the relevant sections of the guidelines referred to in P.III.A., the European Commission~~
~~619 Guideline on the Summary of Product Characteristics[11] and the European Commission Guideline on the~~
~~620 Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[12] are applicable.~~
~~621 For communication regarding pregnancy for vaccines, GVP Chapter P.I should be applied too.~~

~~622 GVP Module XV provides an overview of different means of communication and stresses the importance~~
~~623 of defining communication objectives. The specific communication objectives discussed for medicines~~
~~624 which may be used by women who are of child-bearing potential, planning a pregnancy, or are~~
~~625 pregnant or breastfeeding, relate to enabling women and healthcare professionals to take informed~~
~~626 therapeutic decisions for preventing negative impact of maternal use of medicines on the child,~~
~~627 preventing unnecessary pregnancy terminations, promoting adherence to RMM and supporting~~
~~628 informed choices where the wish for a child exists.~~

~~629 Communication therefore needs to address the specific information needs of women and healthcare~~

[25] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf

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

~~professionals in these different possible clinical scenarios. It is encouraged to also consider that monitoring news and/or social media directed at pregnant and/or breastfeeding women may provide~~

~~11 https://ec.europa.eu~~
~~12 https://ec.europa.eu~~

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

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

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

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

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

~~666~~657 *P.III.B.~~7~~8. Risk minimisation measures*

658 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).

659 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).

~~667 In the area of pregnancy and breastfeeding, the objective of risk minimisation measures (RMM)~~

generally is to reduce any risk to the child as much as possible given the need for appropriate treatment for the mother. In this area, strategies for RMM include those aiming at:

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

- Mitigating the risk in the event of unplanned pregnancy by switching or discontinuing the medicinal product where possible (which may require specialist consultation) and intensified monitoring of the pregnancy;

- Modifying medication before or during pregnancy, e.g. by changing the dosage or route of administration or adapting treatment to the physiological changes in pregnancy for example in the case of medicines with a narrow therapeutic window;

- Where harm to the embryo or foetus by transfer through semen is an identified safety concern, minimising exposure via male partners exposed to the medicine by use of barrier contraception, avoidance of donation of sperm and informing the physician if the partner becomes pregnant;

- Minimising exposure through breast milk by optimised timing of medicine intake, short treatment duration, discontinuation of medication or if minimising exposure is not feasible or acceptable, avoiding breastfeeding. If the decision is taken to breastfeed whilst continuing maternal medicine intake and there is a (potential) risk for the child, the infant should be carefully monitored and breastfeeding discontinued in the case of the adverse signs and symptoms;

- In breastfeeding women, depending on the therapeutic context and the availability of therapeutic alternatives, avoiding use of medicines that significantly reduce breast milk production.

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

P.III.B.7.1. Educational materials

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

- Information regarding the risks and/or uncertainties in relation to exposure *in utero* or through breastfeeding, the risks of the underlying medical conditions, considerations for women of child bearing potential to use adequate contraceptive measures, advice about dosing, switching or discontinuation of treatment, monitoring of the foetus/child or other RMM;

- Information for healthcare professionals to support their communication about risks and RMM with female patients (or their parents/carers);

- Information for women (considering) using the product that explains the risks and the need to consult their healthcare professional to establish the most appropriate treatment and monitoring options for them individually;

- Encouragement of healthcare professionals and pregnant women to report exposure and pregnancy outcomes or suspected adverse reactions in a (breastfed) child to, as appropriate, a pregnancy registry (possibly with follow-up into breastfeeding), teratology information centre, competent authority or marketing authorisation holder (with contact details provided).

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

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

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

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

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

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

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

P.III.B.7.3. Pregnancy prevention programme

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

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

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

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

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

~~659~~660 P.III.C. Operation of the EU network

~~660~~661 *P.III.C.1. ~~Submission of period~~Periodic safety update reports in the EU*

662 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.

663 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.

664 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[27].

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

~~763~~ **Table P.III.2.: Table for reporting numbers of individual case safety reports (ICSRs) in periodic safety update reports (PSURs)~~[13]~~**

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

[27] The rate ~~is usually compared to external reference data which can give an indication on whether the rate is higher than expected.~~

~~Total~~											

Pregnancy outcome	Prospective cases[28] Number					Retrospective cases[29] 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										
Induced termination (congenital anomaly)[30] (specify major congenital anomaly in brackets)										
Elective termination (no congenital anomaly or unknown)										
Stillbirth with congenital anomaly[30] (specify major congenital anomaly in brackets)										
Stillbirth without fetal defects										
Live birth with congenital anomaly[30] (specify major congenital anomaly in brackets)										
Live birth without congenital anomaly										
Unknown										
Total										

~~771~~764 *P.III.C.2. Post-authorisation safety studies in the EU*

765 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[31]. 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

[28] 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.
[29] 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.
[30] The observed phenotype should be specified.
[31] 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)

governance, is available in the HMA-EMA Catalogues of Real-World Data Sources and Studies[32].

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[33]. The latter is an obligation on marketing authorisation holders for all imposed PASS and encouraged for all other PASS (see GVP Module VIII).

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

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

[14] The observed phenotype should be specified.

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

[32] Homepage | HMA-EMA Catalogues of real-world data sources and studies (europa.eu)

[33] Catalogue of RWD studies | HMA-EMA Catalogues of real-world data sources and studies (europa.eu)

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

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

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

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

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

A. GENERAL INFORMATION

- Prospective / retrospective case
- Date of initial contact with marketing authorisation holder
- Source of information ('reporter qualification' in ICH-E2B~~;~~ (R3); a more specific description can be provided in the case narrative e.g. pregnant woman, primary care physician, obstetrician, paediatrician, other)
- Identification of reporter
- Additional identification of the gynaecologist-obstetrician (if reporter is the patient or the primary physician), and the address of the place where the mother ~~plans to deliver~~delivered

B. MATERNAL INFORMATION

- Identification of the pregnant woman receiving the medicinal product ~~patient~~
- Date of birth (or age)
- Weight, height

Obstetrical history

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

~~elective termination with specification of gestational length and context, late foetal death, ectopic pregnancy, molar pregnancy)~~

~~814~~813- Previous maternal pregnancy complications

~~815~~814- Previous foetal/neonatal abnormalities and type

~~816~~815 - ~~History of subfertility~~

~~817~~816 Maternal medical history

~~818~~817 Risk factors for adverse pregnancy outcomes including environmental, occupational, substance abuse
~~819~~818 exposures and medical disorders such as hypertension, diabetes, seizure disorder, thyroid disorder,
~~820~~819 asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted
~~821~~820 disorders, hepatitis, AIDS (specify viral load, CD4 count), and other, including other predisposing
821 factors for neurodevelopmental disorders (NDD).
822 - History of subfertility

823 Current pregnancy

- First day ~~Date~~ of last menstrual period (LMP)
- Gestational age at the time of the first contact with marketing authorisation holder ~~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

- Contraceptive method used

- 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
- Labour / 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

~~856~~857 **D. NEONATAL/INFANT/CHILD INFORMATION**

~~857~~858 Initial

~~858~~859 - Source of information

~~859~~860 - Date of receipt of information

~~860~~ - Outcome of pregnancy and date (~~ectopic pregnancy, molar pregnancy, miscarriage, elective~~
861 ~~termination, late foetal death and~~ stillbirth, live birth)

862 - Date of birth

863 - Gestational age at birth

864 - ~~Gender~~ Sex of neonate

865 - Results of neonatal physical examination including:

866 ⇒ Weight at birth

867 ⇒ Length, head circumference at birth

868 - Malformation/anomalies diagnosed in a foetus or at birth

869 - Conditions at birth (including Apgar scores at 1 and 5 minutes, need for resuscitation, admission
870 to intensive care unit)

871 - Dysmaturity

872 - Neonatal illness, hospitalisation, drug therapies

873 Withdrawal syndrome

874 - Neonatal death (date)

~~872~~875

~~873~~876 Follow-up

~~874~~877 - Source and date of information

~~875~~878 - Malformation/anomalies diagnosed and (cyto)genetic testing results obtained since initial report

~~876~~879 - Developmental assessment

877 - Infant illnesses, hospitalisations, drug therapies, breastfeeding

878

879 **E. EMBRYO/F~~O~~ETAL INFORMATION in the case of ~~elective termination~~TOP, TOPFA, miscarriage and stillbirth~~spontaneous abortion and late~~**
880 **~~foetal death~~**

~~881~~879 - Source of information

~~882~~880 - Date of receipt of information

~~883~~881 - Reason for termination

~~884~~882 - Gestational age at termination

- Results of physical examination (gender, external anomalies) and pathology

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

Risk of pregnancy should be assessed prior to each teratogen prescription

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

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

- The duration of teratogen prescriptions may need to be shortened for patients who use contraceptive methods that require frequent pregnancy testing. 902

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

		affect efficacy[3]	
	Other methods or no contraception	Any duration of use of other methods	Yes + review / refer for contraceptive advice;
		No contraception	Assess need for contraception + test if any suspected risk of pregnancy + review / refer for contraceptive advice;

Explanatory notes:

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

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.
	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)	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.

ICH-E2B(R3) data element	Inclusion/exclusion criteria	Rationale
	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)	
	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) *OR* HLGT "Menstrual cycle and uterine bleeding disorders" *OR* HLT "Contraceptive methods Female" *OR* PT "No adverse reaction"	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 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.

ICH-E2B(R3) data element	Inclusion/exclusion criteria	Rationale
	OR PT "Ectopic pregnancy with contraceptive device" *OR* PT "Ectopic pregnancy under hormonal contraception"	

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