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Guideline on risk assessment of medicinal products in human reproduction and breastfeeding: from data to product information

Draft

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Guideline on risk assessment of medicinal products in human reproduction and breastfeeding: from data to product information

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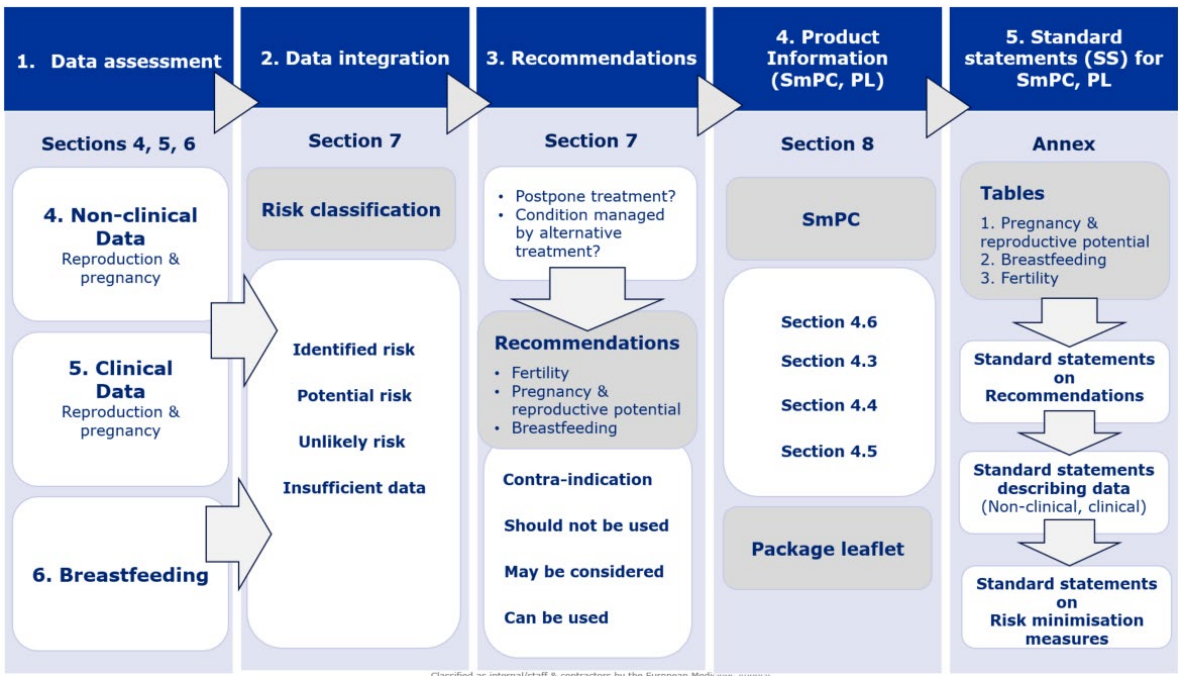
Executive summary

Integrating non-clinical and human data to assess risks of medicinal products for human reproduction, development and if used during breastfeeding is essential. Reflecting this assessment and subsequent recommendations, in the product information of a medicinal product is also important to support informed decisions by health care professionals and individuals using the medicinal product, and to reduce adverse outcomes following use in these populations.

This is the first revision of the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling. The main aim of this revision was to reflect current standards regarding non-clinical - including the option for new approach methods (NAMs) - and clinical assessments. The latter relate to different types of clinical studies, including pharmacoepidemiologic studies, as well as other types of post marketing data. Further details on risk classifications and how these impact recommendations for use of medicinal products during pregnancy, in individuals of reproductive potential, and in breastfeeding are included. Examples of standard texts (statements) for the Summary of Product Characteristics (SmPC) have been updated, and new standard statements on fertility, as well as new standard texts for the Package Leaflet (PL) have been added.

The guideline describes a stepwise process, starting with two sections on assessment of non-clinical (section 4) and clinical data regarding human reproduction and development (section 5), followed by a section on assessment of non-clinical and clinical data in relation to breastfeeding (section 6). Thereafter, a section on integration of non-clinical and clinical data follows (section 7.1), which describes general principles including classification of risks across areas, and provides guidance on recommendations for use for each specific area (section 7.2). The guideline ends with a section on reflections for the product information (section 8, both the SmPC, and PL) as well as an Annex covering standardised texts for data description, recommendations and risk minimisation measures in relation to pregnancy, individuals of reproductive potential and breastfeeding. Figure 1 describes the structure of the guideline and the process it is intended to cover.

Figure 1. Stepwise process of risk assessment: from data to product information



1. Introduction (background)

The information and recommendations on how to use a medicinal product in relation to human reproduction, pregnancy or breastfeeding should enable health care professionals to manage different circumstances, and support individuals in making informed decisions. These situations include prescribing medicinal products to individuals of reproductive potential[1], or pregnant and breastfeeding individuals. Therefore, the product information (PI), specifically the SmPC and PL, should present the available evidence on identified and potential risks related to fertility, pregnancy, and breastfeeding, together with recommendations on the use of the medicinal product in these populations as appropriate, and on the management of risks in clinical practice.

Evaluation of effects on human fertility (male and female) frequently relies on findings from non-clinical studies (reproductive toxicity studies and/or repeated dose toxicity studies), along with knowledge on the mechanism of action and relevant clinical evidence of the active substance(s).

For pregnancy, the risk assessment is based on an integrated and continuous evaluation of clinical experience and non-clinical toxicology, pharmacology and pharmacokinetic data.

During medicinal product development, and early post marketing period, non-clinical data are of great importance since clinical experience is still lacking or limited in most clinical settings. In certain situations, pregnant and/or breastfeeding individuals may be included in clinical trials [1], depending on the medical condition being studied, as well as on the potential risk profile of the substance, or such studies are undertaken with an aim to characterise use of a medicinal product in pregnant individuals. Generally, clinical data becomes more abundant in the post marketing phase as real-world experience with the medicinal product increases, and such data are essential to fully characterise safety in humans. When formulating recommendations with respect to use in females of reproductive potential and during pregnancy, the potential risk of adverse embryo-fetal or infant outcomes due to *in utero* exposure should be weighed against the risk of not treating the pregnant individual.

For breastfeeding, the potential risk to the infant should be weighed against the known benefits of breastfeeding itself. Risk assessment should preferably be based on human data, including concentrations of the active substance (and/or metabolites) in breast milk, estimated exposure of the breastfed infant, the toxicity profile of the substance and suspected adverse effects in breastfed infants. Data on pharmacokinetic properties and certain non-clinical data can support the assessment.

2. Scope

This guideline applies to medicinal products for human use. The purpose of this guideline is to:

- Describe the process for integrating non-clinical and clinical data, and to highlight key factors in assessing the risk of adverse reproductive and developmental effects in humans. This includes effects on fertility and on pregnancy, including effects on the embryo/fetus or child health following exposure during pregnancy, and effects on the breastfed infant.
- Outline how to describe available data, including potential or identified risks, and recommendations for the use of a medicinal product, including relevant risk minimisation measures, in the SmPC and the PL. Standard statements are provided.

[1] In this guideline, terminology relating to sex and gender is selected according to the context and population described. Sex-specific terms (e.g. female, male) are used where necessary for the understanding, such as fertility or for individuals of reproductive potential. Gender-neutral terms (e.g. individuals) are used when referring to those who are pregnant or breastfeeding. "Females of reproductive potential" refers to all females who are able to become pregnant, including adolescents. The term "individual" refers to a person using, or considering the use of, a medicinal product for treatment or prevention.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998 (ICH S6(R1))
- Guideline on detection of reproductive and developmental toxicity for human pharmaceuticals (EMA/CHMP/ICH/544278/1998 (ICH S5)
- Guideline on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (EMA/CHMP/ICH/126642/2008 (ICH S2)
- Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies (CPMP/ICH/384/95 (ICH S3A)).
- Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)
- SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020)
- ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)
- ICH guideline M3 (R2) - questions and answers (EMA/CHMP/ICH/507008/2011)
- Guideline on inclusion of pregnant and breastfeeding individuals in clinical trials (EMA/CHMP/ICH/149462/2025 (ICH E21)
- Guideline on good pharmacovigilance practices (GVP): Product- or population-specific considerations III: Pregnant and breastfeeding women and their children exposed in utero or via breastmilk (EMA/653036/2019)
- Recommendations related to contraception and pregnancy testing in clinical trials, CTCG Clinical Trials Coordination Group
- GVP Module V – Risk management systems (EMA/838713/2011)
- GVP Module XVI Addendum I – Risk minimisation measures for medicinal products with embryo-fetal risks (EMA/608947/2021)
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology (EMA/95098/2010)
- ENCePP Annex 2 to the Guide on Methodological Standards in Pharmacoepidemiology
- Guideline on the Summary of Product Characteristics. Rules governing Medicinal products in the European Community Volume 2C The Notice to Applicants

4. Non-clinical assessment of risk to human reproduction and development

4.1. Introduction

Developmental and reproductive toxicity (DART) studies aim to detect effects of a medicinal product on mammalian reproduction and development. They typically consist of a fertility and early embryonic development (FEED) study, embryo-fetal development (EFD) studies in two species (rodent and non-rodent), and a pre- and postnatal development (PPND) study. However, this standard approach may be adapted according to various factors including the type of medicinal product, target population, knowledge of pharmacological target(s) and its(their) role in reproduction and development.

Results of other non-clinical studies and weight of evidence (WoE) approaches should also be considered as they may significantly influence the testing strategy and/or risk assessment. See ICH S5(R3) guideline [2] for further details on these aspects. Regarding risk assessment for breastfeeding, see section 6.

For the non-clinical assessment, reproductive and developmental toxicity includes:

- Effects on reproduction in the parental generation (i.e. fertility): any adverse effects (structural and functional) on the male and/or female reproductive organs or on the related endocrine systems including amongst others: gamete production and transport, reproductive cycle, mating behaviour, or modification of other functions that are dependent on the integrity of the reproductive system.
- Effects on development in the progeny: any adverse effects (structural and functional) on the conceptus resulting from prenatal exposure or induced during the suckling period or manifested postnatally (adverse effects on e.g. behaviour and / or sexual maturation).

4.1.1. Choice of species

The rat is a common rodent species in all types of DART studies (FEED, EFD and PPND), whereas the rabbit is a common non-rodent second species for the EFD study. For the EFD studies, at least one of the selected species should be responsive to the primary pharmacodynamic effect of the medicinal product. In addition, the pharmacokinetic profile, including biotransformation, should enable assessment of the relevance of the species selected for DART testing and thus an extrapolation of the results from animals to humans.

In cases where the rat or rabbit are considered unsuitable for testing due to e.g. lack of pharmacological and/or pharmacokinetic relevance or tolerability issues, an alternative rodent or non-rodent species should be considered. Other options including the use of genetically modified animals or a species-specific surrogate molecule may also be considered provided that pharmacological relevance is ensured. When no relevant species can be identified, the impact of this deficiency should be discussed in the assessment report and considered for the recommendations in the SmPC and PL.

4.1.2. New approach methods

NAMs, including alternative *in vitro*, *ex vivo*, and non-mammalian *in vivo* assays may be valuable to identify adverse effects or to contribute to the understanding of the mechanisms underlying developmental and reproductive toxicity at any stage of medicinal product development. These methods when qualified for context of use may also support risk assessment and, where justified, reduce or replace certain *in vivo* studies. Further details are provided in the ICH S5(R3) guideline [2].

4.1.3. Route of administration

The route of administration used in DART studies should generally be the one intended for human use. An alternative route may be acceptable if a similar or 'better' pharmacokinetic profile (i.e. resulting in higher exposure) can be demonstrated.

4.1.4. Dose regimen/scheme

The dose range tested in DART studies should have covered a dose resulting in minimal maternal toxicity such as e.g. decreased body weight or food consumption or, at the high dose, result in a 25-fold exposure margin compared with the estimated human exposure at the maximum recommended

dose. See ICH S5 guideline [2] for more details. While determining a "no observed adverse effect level" (NOAEL) is desirable, dose levels should be chosen to reveal dose-related trends. Dose levels leading to serious maternal and/ or offspring toxicity, including mortality, can mask a potential for developmental toxicity.

It should be evaluated whether the applied dose intervals/frequencies achieve sufficient exposure during the sensitive periods under study and are clinically relevant.

4.1.5. Pharmacokinetics/toxicokinetics

Exposure in pregnant animals to the active substance(s) and/or major human metabolite(s) (≥10%) [2-5], should be assessed. Indirect estimation of exposure in pregnant animals, based on toxicokinetic data from non-pregnant animals from the same species used in different repeated toxicity studies represents an element of uncertainty.

When available, information regarding placental transfer of the active substance (and/or metabolites) can be of value for the assessment.

4.1.6. Mechanism

Toxicants can disrupt reproduction and/or development through maternal/paternal toxicity, direct effects on the conceptus (placenta, extraembryonic membranes, or embryo/fetus), indirectly via maternally mediated effects, or a combination of both. Thus, substances not able to cross the placenta can still cause embryo-fetal toxicity due to indirect alterations of maternal physiology (e.g. hyperglycaemia).

If reproductive and/or developmental toxicity has been identified, an understanding of the molecular basis (i.e. mechanism of action) to support a biologically plausible explanation for the observed toxicity, together with interspecies comparisons of the pharmacological effect, is of value for risk assessment. Mechanistic data can include information on pharmacokinetics, interactions with fertility and developmental processes in the mother (hormonal disruption, cytotoxic effects, inhibition of angiogenesis essential for ovarian function, placental development, embryonic growth), embryo/fetus or extraembryonic tissues. Since medicinal products are often targeted towards a well-defined biological entity (receptor, ion-channel, protein etc.), the on-target molecular interaction is usually known. However, the actual embryo-fetal exposure, including time point for exposure in relation to the sensitive period of development of a specific organ/tissue, will influence the final outcome.

A WoE evaluation (see section 4.2.) is an important part of human risk assessment since it is acknowledged that it can be difficult to generate data in sufficient detail for a clear understanding of both mode of action, and mechanism of action behind embryo-fetal toxicity, especially for a new chemical entity from a new class, and within the remit of regulatory testing. This is due to the complexity of normal development, a multitude of interaction points for a substance, and since mode of action understanding involves several levels of biological organisation.

For gene therapies or vaccines using genetically modified viral vectors that are replication-incompetent, the risk of vertical maternal and paternal germline transmission of vector DNA, should be assessed. See Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors [6] for more details.

4.1.6.1. Genotoxicity

Results of comparative studies have shown that, in a qualitative sense, most germ cell mutagens are likely to be detected as genotoxic in somatic cell tests. If positive genotoxic effects are identified in the

genotoxicity battery tests (See ICH S2 [7]), this also raises concerns for reproductive and developmental effects (both at gamete level as well as the embryo, depending on the exposure time). See "Safety Working Party (SWP) recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020)" [8] for further details.

4.1.7. Multigenerational studies

Reproductive studies evaluating drug-related effects over generations may be available in exceptional circumstances. Particular attention should be paid to the robustness of the study design to meet the study objectives driven by substance specific potential safety concerns. The clinical relevance of the reported findings should be considered in the context of all other available non-clinical and clinical data (including mechanistic studies).

4.2. Evaluation process

The non-clinical assessment should be based on all pharmacological (primary, secondary and safety), pharmacokinetic and toxicological data available. In some situations, all elements from standard reproductive toxicity testing may not be available or are not warranted. A WoE approach can in these cases be adequate to support decision-making when evaluating reproductive and developmental risk. Such approaches use the totality of evidence available, and take into account literature data, class effect data and data from alternative models or NAMs such as (complex) *in vitro* models or *in silico* models, as well as all available relevant non-clinical and clinical data for the substance. The severity of the disease, therapeutic indication, the target population and other relevant risk factors should also be taken into account.

In this context, WoE approaches are particularly useful to demonstrate presence of risk. However, if the data are sufficiently robust and substantiated, a WoE evaluation to support the likelihood of absence of risk can be accepted on a case-by-case basis.

4.2.1. Uncertainties from available data

The representativeness, completeness, strengths and weaknesses of available data sets should always be considered in the evaluation process. If some non-clinical studies (including reproductive toxicity) are lacking, or some studies are irrelevant, or if data on certain endpoints are lacking, the impact of such insufficient data should be addressed in the evaluation and considered for the overall conclusion on developmental and reproductive risk.

4.2.2. No effect detected

If appropriately designed developmental and reproductive toxicity studies with adequate systemic exposure do not indicate direct or indirect harmful effects, and there are no relevant effects identified in other pharmacological or toxicological studies, this conclusion enables finalisation of the non-clinical evaluation process.

If no findings are observed for a substance belonging to a class where adverse effects are expected, this may need further clarification.

4.2.3. Effects detected or known

If an effect suggesting reproductive and/or developmental toxicity is detected, the evaluation process should continue as outlined below in order to assess the level of concern.

There are several contributory elements that may affect the level of concern. The following aspects should be taken into consideration:

4.2.3.1. General aspects

- Recognition of an effect

Statistically significant differences between treatment and control groups alone do not necessarily indicate a safety concern, nor does lack of statistical significance impute absence of an effect. Other criteria of importance include biological plausibility, reproducibility, medicinal product- or species-specific mode of action, relationship to an animal-specific metabolite, the magnitude and nature of the effect and/or clear dose-response relationship. Furthermore, reproductive toxicity studies usually lack statistical power to detect subtle increases in rare events. Thus, an increased frequency of rare events in exposed animals in comparison with the study control as well as with recent historical control data from the same strain and preferably from the laboratory in which the study was performed, may increase the concern for reproductive toxicity in humans.

- Inter-species concordance

Even if adverse findings from only one species can raise serious concerns, if similar effects are observed in more than one species, it may increase the concern for developmental and/or reproductive toxicity in humans. Inter-species concordance is most likely to be identified for structural birth defects/congenital anomalies, or histopathological examinations of reproductive organs, because these endpoints are studied in multiple species.

- Type of effects

Structural birth defects/malformations and embryo-fetal lethality have more weight in estimating a concern for developmental toxicity in humans, than general effects (e.g. growth retardation and variations, as delays in ossification). The latter, possibly reversible effect(s), might be induced by maternal stress or other maternal toxicity.

Data from reproductive toxicity studies and/or from repeated dose toxicity studies in sexually mature animals may suggest detrimental effects on fertility. In repeated dose toxicity studies, such effects could be alterations to endocrine function or histopathological changes in the gonads or genital organs, which may be detected in both rodents and non-rodents. Further understanding of possible mechanisms is desirable for risk assessment.

- Multiplicity of effects

Multiplicity of effects usually increases concern for reproductive toxicity in humans. Multiplicity refers to the observation, in a single species or animal model, of two or more effects with related biological endpoints in fetal examinations, e.g. abnormally shaped vertebrae plus abnormal number of vertebrae would give rise to increased concern, more than just a single observation with regards to vertebral development.

- Adverse effects at various stages of the reproductive process

This refers to observations in a single species or animal model, of effects during different stages of the reproductive process, e.g. increased early intrauterine death plus some malformations would give rise to increased concern with regards to developmental toxicity.

- Maternal toxicity

If developmental toxicity is seen only at maternally toxic dose levels, further understanding of potential causality between maternal and developmental toxicity is desirable. From a regulatory

perspective, claims that developmental toxicity is due to maternal toxicity should be adequately justified. Further, there needs to be support that such findings do not have clinical relevance (e.g., by providing mechanistic data in support of maternal toxicity being the reason for the observed developmental toxicity).

4.2.3.2. Specific aspects

- Animal to human exposure ratio

This should be based on the systemic exposure of the animal at the NOAEL for reproductive toxicity and the systemic exposure in human at the maximum therapeutic dose. In case of serious embryo-fetal outcomes in the animal studies, estimations of animal and human exposure ratios at doses associated with malformation or embryo-fetal lethality can provide further insight for the risk assessment.

When reporting animal data in SmPC section 4.6, a tiered system on how to interpret NOAEL for EFD toxicity testing should be taken into account [2]. In general, there is increased concern when the NOAEL occurs at exposures less than 10-fold the human exposure at the maximum recommended dose. Above this threshold, concern is reduced, and effects observed at 25-fold or larger exposure margins are usually of minor concern for clinical use.

- Neurodevelopmental risk assessment

The entire nervous system, including the central nervous system (CNS) undergoes continuous complex multifactorial development from early embryogenesis through to adulthood. From a non-clinical perspective, the risk assessment should take into account the totality of available evidence namely pharmacology, pharmacokinetics and toxicology data. Nevertheless, non-clinical models may not fully reflect the complexity of human neurodevelopment, which needs to be considered in the assessment. In particular, the clinical relevance of finding(s) from neurobehavioral tests conducted in the PPND studies, should be thoroughly interpreted in combination with the overall human risk assessment.

5. Clinical assessment of risk to human reproduction and development

5.1. Introduction

The clinical assessment will generally be based on various types of clinical data. These could include case reports, case series, clinical trials, and epidemiological studies and originate from different sources, e.g. electronic healthcare records, pregnancy registries, registries of congenital anomalies, and spontaneously reported post-marketing data.

The assessment should consider the scientific quality and robustness of available data, methodology for data collection, study designs, the clinical context such as target population, and the amount of available data.

5.2. Effects on fertility

Fertility refers to the ability of an individual (male or female), a couple, or a population to reproduce. Infertility is defined as a disease of the male or female reproductive system characterized by the failure to achieve a clinical pregnancy after one year or more of regular unprotected sexual intercourse [9]. Clinical evaluations of fertility typically focus on couples who meet this criterion.

Medicinal products may impair fertility of males and/ or females, through various mechanisms such as hormonal disruption or cytotoxic effects. Effects may be reversible or permanent. The pharmacological properties of the medicinal product, together with the characteristics of the target population, will guide the most appropriate approach to assessing potential adverse effects on fertility.

Evaluation of fertility may include, but is not limited to, assessing effects on hypothalamic/pituitary gonadal function, as well as effects on the reproductive organs/tissues. In addition, impairment of implantation or an increased occurrence of early spontaneous abortion, are other relevant fertility markers. Surrogate markers of fertility may be appropriate and can be studied on a case-by-case basis. Studying effects on fertility by monitoring reproductive outcome in couples is generally considered difficult due to practical and methodological challenges.

5.3. Effects on pregnancy

5.3.1. Adverse pregnancy outcomes

The administration of a medicinal product during pregnancy may cause various adverse effects in the (unborn) child, including morphological, and/or functional developmental disturbance in the embryo or fetus - whether detected at birth or not – as well as embryonic or fetal death. The nature and severity of these effects depend on different factors including timing of exposure during critical phases of development. Also, the maternal disease being treated may in itself affect embryo/fetal development adversely, which needs to be taken into account.

Main types of adverse pregnancy outcomes include:

- Non-live birth, including spontaneous abortion (miscarriage) and fetal death
- Congenital malformation
- Embryotoxic and/or fetotoxic effects
- Neonatal outcomes
- Neurodevelopmental disorders (NDD)

In addition, some effects fall outside these categories (e.g. transplacental carcinogenesis). For detailed description/definition of "susceptible periods" and "adverse pregnancy outcomes" see "Guideline on good pharmacovigilance practices (GVP) Product- and Population- Specific Considerations III: Pregnant and breastfeeding women and their children exposed *in utero* or via breastmilk" [10].

5.3.1.1. Non-live birth, including spontaneous abortion (miscarriage) and fetal death

Non-live births include spontaneous abortion/miscarriage (early fetal death, that occurs before 20 completed weeks of gestation), stillbirth (late fetal death, that occurs after 20 completed weeks of gestation). Also, termination of pregnancy due to embryo-fetal abnormalities is included in this group of events. Incomplete capture of early pregnancies because pregnancies may not be immediately recognised makes precise estimation of spontaneous abortion frequencies uncertain but is about 25% of all pregnancies. This frequency increases with maternal age. Stillbirths are reported to occur in about 0.3% of total births in Europe (range: 1.8-4.7 per 1000) [11].

5.3.1.2. Congenital malformation (birth defects)

Congenital malformation[2] are structural anomalies of organs, systems, or parts of the body that occurs during intrauterine development and may be associated with altered organ or system function. A congenital malformation may result from genetic factors or from exposures to an environmental factor including medicinal products. Congenital malformations can have significant medical, surgical, or cosmetic consequences.

While it may be possible to diagnose some congenital malformations prenatally, others will only be captured during the first years of life, leading to higher prevalences with longer follow-up after birth. Additionally, in studies restricted to live births, risks may be underestimated if the medicinal product caused pregnancy losses (i.e. live-birth bias, see [12,13]), or if the pregnancy is terminated due to major malformations detected *in utero*. Prevalence also varies depending on how major malformations are defined in the data source. In Europe, the EUROCAT classification system provides a harmonised framework for categorizing congenital malformations across data sources, assigning major or minor status to specific conditions within organ systems [14]. Additional factors, such as the inclusion or exclusion of minor malformations or those due to genetic diseases, will also impact reported prevalence. Prevalence estimates may also differ depending on whether exposure information is collected prospectively (before pregnancy outcome is known, either adverse or non-adverse) or retrospectively (after the outcome), the latter being more susceptible to recall bias. The live birth prevalence of major congenital malformations is reported to be 2–4% in Europe [14] and 3-5% in the United States [15].

5.3.1.3. Embryotoxic and/or fetotoxic effects

Embryotoxic and/or fetotoxic effects include impaired fetal growth (low/very low birth weight, small for gestational age or intrauterine growth restriction), excessive growth (large for gestational age or fetal macrosomia), and adverse effects on organs (e.g., endocrine or reproductive organs). Embryotoxicity refers to effects from exposure during the first trimester, while fetotoxicity generally refers to exposure in the second and/or third trimester.

5.3.1.4. Adverse neonatal outcomes

Adverse neonatal outcomes generally reflect pharmacological effects of the medicinal product during late pregnancy or around the time of delivery, while preterm births, neonatal and infant death also can belong to this category. For example, exposure to immunomodulating or immunosuppressive substances may increase the risk of infections in the newborn. Other examples include neonatal withdrawal syndrome resulting from sudden discontinuation of exposure to a medicinal product (e.g. opioids), or persistent pulmonary hypertension of the newborn (PPHN), following exposure to serotonergic or vasoconstrictive substances. The likelihood and severity of these effects depend on the pharmacological properties of the substance, the timing, degree and duration of exposure, and the developmental stage at which the fetus is exposed.

5.3.1.5. Neurodevelopmental disorders (NDD)

The entire nervous system, including the CNS, remains vulnerable to neurotoxic effects throughout pregnancy. Accordingly, *in utero* exposure to medicinal products may impact on neurodevelopment, even in the absence of structural anomalies. A consensus definition of NDD is not available, however the International Classification of Diseases ICD-11 [16] defines NDD as behavioural and cognitive disorders with onset during the developmental period before 18 years of age, impairing intellectual,

[2] Congenital malformation - narrow subset of congenital anomaly - is used for errors in morphogenesis excluding disruptions or deformations. Birth defect refers to the observable structural anomalies that are present at birth (GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women and their children exposed *in utero* or via breastmilk [10])

motor, language, or social functions. Examples include intellectual disability, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and learning disorders. These outcomes are important considerations in the long-term safety assessment of medicinal products used during pregnancy.

Risk assessment of NDDs following prenatal medicinal product exposure typically relies on human observational studies, as non-clinical models may not fully reflect the complexity of human neurodevelopment. Such studies should use validated measures to assess neurodevelopment, and different types of NDDs should be analysed separately. Combining heterogeneous conditions (e.g. ADHD, ASD, intellectual disability, and learning disorders) into a single composite outcome is problematic because they differ in aetiology, developmental course, and measurement, which can distort risk estimates and obscure clinically meaningful, condition-specific effects. Further, given the potential for delayed diagnosis of exposure-related NDDs, sufficient follow-up periods to detect outcomes that may only emerge later in childhood are needed. The minimum follow-up period should preferably exceed the upper quartile of the median age at diagnosis, i.e. the age by which approximately 75% of affected children have been diagnosed, in the relevant country or setting. Study designs must also account for the multifactorial nature of NDDs and the role of maternal, paternal and child covariates, including relevant environmental factors, in the relationship with the exposure of interest, and control for potential confounders to ensure the reliability and interpretability of results. Consideration as to the role of different methods of ascertainment in geographical or temporal differences in rates of NDD may also be warranted. As a consensus definition for NDD is not available, particular attention should be given to the definition of NDD and its components in any given study or data source.

5.3.2. Clinical assessment of data on pregnancy outcomes

For clinical assessment of outcomes of exposure to a medicinal product during pregnancy, available sources of evidence are often non-interventional. However, in certain situations, pregnant individuals may be included in clinical trials [1], depending on the medical condition being studied, as well as on the potential risk profile of the substance, or such studies are undertaken with an aim to characterise use of a medicinal product in pregnant individuals. Evaluation of clinical trials follows standard methodology, as appropriate for the specific trial.

Given the variation in background prevalence for adverse pregnancy outcomes, and methodologies across data sources and studies, using an appropriate control group from the same data source, as well as similar duration of follow up, is desirable, and should be aimed for, if feasible, to facilitate valid comparisons and a fulsome assessment.

For non-interventional pregnancy studies, several common biases need to be considered [12,13]. These issues can distort results but can, at least to a certain extent, be addressed through careful study design, appropriate timing definitions, and sensitivity analyses as outlined below:

Ascertainment of exposure to the medicinal product in pregnancy:

- Spontaneous and solicited reports may be reported prospectively, in which exposure to the medicinal product is reported before the pregnancy outcome is known, either adverse or non-adverse and prior to any prenatal investigation. In contrast, retrospective reports involve cases where exposure is reported after the outcome is already known. While retrospectively reported pregnancies should not be excluded from the assessment, an analysis restricted to prospectively reported pregnancies avoids recall bias.

- Timing and degree of exposure to the medicinal product during pregnancy relative to susceptible periods should be considered. For instance, where pregnancies are exposed late in the first trimester, organogenesis may have already been completed and their capture as exposed pregnancies may bias a harmful effect towards the null. Pharmacokinetics including half-life and placental transfer should be considered in relation to degree of exposure during pregnancy. Furthermore, if exposure occurred prior to conception or the susceptible period for a particular adverse outcome, these parameters have to be considered before excluding exposure to the medicinal product as relevant to the adverse pregnancy outcome of interest.

- When comparing adverse pregnancy outcomes following exposure to a medicinal product which occurs after conception with those among pregnancies without such exposure, immortal time bias may occur:

  - either when the unexposed 'immortal' (event-free) time spent prior to exposure is incorrectly classified as exposed, leading to underestimated risk among the exposed pregnancies,

  - or the unexposed 'immortal' time prior to exposure is incorrectly excluded from the analysis, leading to an over-estimated risk among unexposed pregnancies and selection bias (pregnancies included in the exposed cohort had to survive without experiencing the adverse pregnancy outcome in order to be exposed to the medicinal product and therefore may differ from those that were never exposed).

  This can be avoided by defining cohort entry at treatment initiation or by using a time-varying exposure definition. Alternatively, a landmark design (e.g., gestational week 12 or 20) may be used, although this can introduce live birth bias by excluding early pregnancy losses.

Ascertainment of the adverse pregnancy outcome:

- The definition of the adverse pregnancy outcome studied, should be considered. Caution is advised in generalising conclusions to subtypes of outcomes or components of a composite outcome not explicitly studied. Population-based studies in real-world data sources may be affected by misclassification, for example due to reliance on a single (diagnostic) code that does not confirm the outcome, overrepresentation of more severe outcomes (e.g. conditions requiring hospitalisation), or underrepresentation of outcomes that may not routinely present to the healthcare system (e.g. early miscarriage, pregnancy termination, or certain minor congenital anomalies).

- The period of follow-up may have important implications. Prevalence of major anomalies increases when infants are followed to 12 months of age rather than being evaluated at birth only. In the context of NDDs, assessing CNS function in early childhood present challenges, as some disorders may not manifest until later in childhood, thereby requiring years of follow up to capture adequately.

Selection bias:

Selection bias in studies of medicinal products exposure during pregnancy can occur when the pregnancies included are not representative of pregnancies in general. This can arise in several ways. For example, left truncation occurs when pregnancies are not observed from conception and need to reach a certain gestational age to be captured in a data source, leading to under-ascertainment of the total number of pregnancies. Live birth bias is another concern and occurs when studies include only live-born infants, potentially underestimating risk if the exposure leads to pregnancy losses that are excluded from analysis. This issue is less relevant in studies of long-term outcomes such as NDDs, which are assessed among live births only. Avoiding selection bias requires careful attention to

inclusion criteria, timing of data capture, and completeness of outcome reporting, especially for early pregnancy losses and non-live births.

Confounding bias:

- Minimising confounding by indication in pregnancy safety studies requires careful study design, particularly in comparator selection and adjustment for disease-related factors. Restricting the study population to pregnant individuals with the same underlying condition—for example, by including a non-medicated disease comparison group—can help control for confounding at the design stage. However, confounding by disease severity may still remain. To address this, researchers can use an active comparator group (e.g. pregnant individuals treated with alternative treatment for the same indication) and apply statistical adjustment for available markers of disease severity and other confounders to strengthen causal inference. Designs where siblings in unexposed and exposed pregnancies are compared may also be helpful.
- Confounding may also arise due to differences between exposed and comparator cohorts in the calendar period over which pregnancies occurred (due to changes in prescribing practices or outcome detection over time) or gestational age over which pregnancies were observed (whereby the cohort observed from an earlier gestational age may be less susceptible to left truncation) and should be addressed.
- The potential causal relationship addressed by the research question including relevant maternal, paternal and offspring covariates, and biological (including the indication) as well as environmental factors should be carefully considered. This should include in particular the impact of unmeasured confounding. It is also important to consider over-adjustment bias and collider (selection) bias that could arise due to adjustment for intermediate covariates occurring or measured during or at the end of pregnancy and after the exposure. Evaluation should be informed by clinical knowledge and relevant literature and may be complemented by causal diagrams.

Required sample size:

There is no predefined number of exposed pregnancies that is sufficient for a reassuring conclusion for any potential risk to the embryo or fetus as this depends on the baseline rate of a particular adverse outcome, and the many factors that influence its detection and reporting. For major congenital malformations (with baseline rates of 3-5%), a few hundred prospectively collected exposed pregnancies, with known outcomes, without a concerning pattern are generally needed to conclude that a manyfold increased risk is less likely.

For stronger reassurance, including lack of increased risk for major congenital malformations in specific organs, data of adequate quality from a few thousand prospectively collected exposed pregnancies, with known outcomes not indicating an increased risk are needed.

For some adverse pregnancy outcomes, where the background rates are more common than for major congenital malformations, smaller sample sizes may suffice.

Observations from different data sources can be pooled provided methodological considerations are considered, for instance use of comparable definitions for the outcomes of interest. The estimated absolute frequency, relative risk or excess risk of an adverse pregnancy outcome following exposure to the medicinal product *in utero* should in general be presented with a confidence interval, where the width of the interval reflects the precision of the estimate.

6. Assessment regarding breastfeeding

6.1. Introduction

Clinical data are essential for characterising safety of a medicinal product for a breastfed infant, and to support recommendations regarding treatment of the mother during breastfeeding. Non-clinical data can be complementary, particularly when clinical data are limited. Milk samples collected from lactating[3] or breastfeeding individuals can be used in studies to quantify medicinal product transfer into human milk, allowing calculation of the relative[4] and/or daily[5] infant dose.

Pharmacokinetics of the medicinal product, in both mother and infant should also be considered. This does not only cover possible transfer into breast milk, but also systemic exposure in the infant (based on intestinal absorption, distribution, metabolism and elimination). Additionally, the pharmacodynamic properties of the medicinal product should also be considered to assess the potential for adverse reactions in the infant during breastfeeding.

Data from follow-up of breastfed infants for potential adverse reactions provides additional valuable insights into the safety of medicinal products during breastfeeding.

Modelling and simulation approaches can be used to leverage sparse human data, primarily through population pharmacokinetic modelling. Physiologically based pharmacokinetic modelling (PBPK) needs qualified models, however since the pharmacokinetics of transfer to breast milk is a complex process and the impact of the model will be high, the feasibility of using such models is currently limited.

Complementary role of non-clinical data

Information regarding excretion into animal milk of the active substance (and/or metabolites) can be of value for the assessment. However, due to interspecies differences in lactation physiology and milk composition, direct quantitative extrapolation of medicinal product concentrations in animal milk to human milk is generally not possible. Non-clinical data alone is generally insufficient to support definitive recommendations in humans, unless the method or model is predictive for human milk transfer or infant exposure/safety in the context of use. In general, recommendations on breastfeeding should be based primarily on human data, while non-clinical data may contribute to risk assessment when adequate human data are lacking, and should be interpreted with caution.

6.2. Risk assessment for a breastfed infant

Major and complementary factors for risk assessment are described below. Their order below does not reflect their relative importance in the assessment process.

6.2.1. Major elements of assessment:

- Breastfed infants' plasma/blood concentrations of the medicinal product, which support direct estimation of systemic exposure.

[3] "Lactating" refers to the physiological production of milk, while "breastfeeding" refers to the act of feeding the infant. In some cases, milk samples may still be collected after breastfeeding has ceased if milk production persists.
[4] Relative infant dose (RID) is the estimated daily dose of a medicinal product received by an infant through breast milk (mg/kg/day), expressed as a percentage of the maternal weight-adjusted dose (mg/kg/day). It provides an estimate of the extent of medicinal product transfer into breast milk. For quantification of risk for the infant based on RID categories see section 8.2.1.2.
[5] Daily infant dose (DID) is the absolute dose of a medicinal product ingested by an infant through breast milk. It provides a direct measure of infant medicinal product exposure during breastfeeding. DID can be compared with the therapeutic daily dose for an infant of the same age and body weight receiving the medicinal product as treatment.

- Estimation of the amount of medicinal product received by infants through breast milk, based on the measured concentration of the active substance /metabolite(s) in human milk, taking into account maternal dose and treatment duration, as well as estimated breastmilk intake by the infant. These could be expressed as a relative infant dose (RID) or a daily infant dose (DID).
- Case reports of adverse effects in breastfed infants, which could be signals of potential safety concerns.
- Follow up of breastfed infants during their mothers' treatment, which supports ongoing safety evaluation and could potentially identify both short-term and long-term effects.
- Pharmacokinetics in the mother (considering route of administration, plasma concentrations and elimination characteristics), in breast milk and in the infant (particularly gastrointestinal absorption and rate of elimination).
- Pharmacodynamic properties and safety profile of the medicinal product, including known class effects and/or data from paediatric use.

6.2.2. Complementary data for assessment:

As major elements of assessment are usually scarce, all complementary data available should be assessed as well.

- The physicochemical properties of the medicinal product, which help estimate the extent of its transfer into breast milk.
- Documented use of the medicinal product during breastfeeding, even without formal follow up of breastfed infants.
- Infant-specific factors, such as age, overall health status and developmental maturity.
- Non-clinical data (e.g., qualified *in vitro* or *in silico* methods, transfer of the medicinal product in animal milk, peri- and post-natal or juvenile toxicity studies) which can support estimation of exposure and risk.

A pharmacological class effect might not always be relevant for risk assessment for breastfeeding infants, as infant exposure can vary substantially between substances within the same class due to differences in their pharmacokinetic properties, leading to differences in risk classification.

Risks from direct dermal exposure to the breastfed child, when there is topical application on the breast or on large skin area should be considered.

6.3. Assessment of effect of a medicinal product on lactation (breastmilk production, secretion and composition)

Some medicinal products can decrease or increase breast milk production by affecting prolactin levels. Others can affect breast milk secretion by affecting oxytocin levels. Additionally, certain medicinal products may impact the composition or quality of breast milk, or other aspects related to breastfeeding. All existing data on these effects should be considered when relevant.

6.4. Proteins including monoclonal antibodies and risk assessment for breastfeeding

Physiological processes (including increased paracellular permeability of the mammary epithelium shortly after delivery) result in therapeutic monoclonal antibodies (mAbs) being present in higher

amounts in the colostrum than in mature milk, with rapidly decreasing levels of the mAb thereafter. Gastrointestinal uptake of mAbs by the breastfed infant is also very low, with some possible exception for preterm infants and neonates. Due to intrinsic properties, mAbs are denatured and rendered inactive following acidification in the infant's stomach, further limiting systemic exposure.

A standard recommendation cannot be given for all mAbs, as safety during breastfeeding depends on substance-specific factors including the extent of breast-milk transfer, the infant's gastrointestinal absorption and the pharmacological mechanism of the mAb. Furthermore, findings from (enhanced) (e)PPND studies, if appropriate (see [2,17,18]), should be considered. However, when the risk profile of the mAb is sufficiently characterised, product-specific recommendations can be made. In some cases, it may be appropriate to restrict breastfeeding only right after birth and to permit breastfeeding, thereafter, based on physiological principles and inherent characteristics of the medicinal product. A similar case-by-case approach may be applicable to other protein-based therapeutics. Standard texts for mAbs or protein-based products with respect to breastfeeding are included in the Annex.

7. Integration: From data to product information

7.1. General principles

The general aim of this section is to guide on how to integrate data from various sources to determine appropriate wording for the SmPC and PL in relation to male and female fertility, for females of reproductive potential, and for pregnant or breastfeeding individuals. Efforts should be made to provide the reasons for the recommendations given. This information is important for the health care professional and for the (to be) treated individual to support an informed decision.

In the overall assessment, available knowledge from all relevant data sources should be considered. This includes clinical experience, pharmacological activity, pharmacokinetic data, results from non-clinical studies, and knowledge about medicinal products within the same class; based on information from e.g. clinical studies (interventional or non-interventional), non-clinical testing (*in vitro* or *in vivo*), spontaneous reporting as well as literature. Aspects such as alternative treatments, impact of the maternal disease on the pregnancy, and clinical practices should also be considered. The more extensive clinical data being available, the less emphasis is put on non-clinical studies in the integration process.

Within each specific area, following an integrated assessment of available evidence and its strengths and limitations, a general risk classification is concluded upon, as follows.

- A risk is considered **identified** if there is sufficient scientific evidence from non-clinical and/or clinical data, and in some instances taking pharmacodynamic effects into account, to conclude, with at least a reasonable possibility, that the adverse outcome is **caused by** the medicinal product.
- A risk is considered **potential** if scientific evidence from non-clinical and/or clinical data, and in some instances taking pharmacodynamic effects into account, suggests **a possible causal relationship** between the adverse outcome and the medicinal product. It can also correspond to insufficient non-clinical and/or clinical data, but where available data raise concerns.
- A risk is considered **unlikely** when a sufficiently large amount of non-clinical and / or clinical data of adequate quality, including knowledge of the pharmacodynamic effects, do not raise concerns for adverse outcomes.
- Available data do not raise specific concerns but are **insufficient** to draw final conclusions.

This overall assessment guides the information, and recommendations, including risk minimisation measures, to be included into the SmPC and PL. The risk classification can also guide risk management planning, as outlined in GVP Module V on Risk management systems [19]. Some guiding elements regarding the risk classification within each specific area are presented below.

The PI, and if appropriate, the recommendations for use in these different populations, should be updated when relevant new data become available.

7.1.1. Fertility

The evaluation of effects on human fertility mostly relies on the outcome of non-clinical studies and knowledge of any effect that could be related to the mechanism of action. If available, clinical data should be integrated in the assessment. Regarding non-clinical studies, the assessment should be based on the results of genotoxicity studies, FEED studies and/or repeat-dose toxicity studies. The latter generally provides important information contributing to further characterise potential effects on fertility based on pathology and functional parameters for both male and female reproductive function.

Evidence of impaired fertility includes abnormal sperm parameters, menstrual or ovulatory disturbances, testicular or ovarian toxicity, reduced conception rates in animals, and additional mechanistic evidence regarding reproductive hormones or germ cell function.

For the assessment of the risk classification, some guiding elements are outlined below:

7.1.1.1. Identified risk for impaired fertility

- Non-clinical data of human relevance and of sufficient quality, and / or clinical data of sufficient quality show a risk for impaired fertility.
- A plausible mechanism of action has been identified that leads to risk for impaired fertility.

7.1.1.2. Potential risk for impaired fertility

- Non-clinical data suggest adverse effects on fertility, but human relevance is uncertain, and there is no or insufficient clinical evidence to conclude causality.

7.1.1.3. Unlikely risk for impaired fertility

- Non-clinical data do not show or suggest impaired fertility and there is no clinical evidence suggesting adverse effects on fertility.

7.1.1.4. Insufficient data with respect to fertility

- Available data do not raise specific concerns but are insufficient to draw final conclusions e.g. non-clinical findings are inconclusive, and clinical evidence is insufficient to fully assess risk of adverse effects on fertility.

7.1.2. Pregnancy

An integrated approach for risk assessment of prenatal exposure and adverse pregnancy outcomes is presented below, in the form of questions adapted from teratological principles [20-22], modern epidemiological reasoning and principles for assessment of medicinal products safety in pregnancy. The order of questions below does not reflect the relative importance of these in the assessment process.

While the reliability of the overall assessment will depend on the extent to which clear and definitive answers to these questions can be obtained, in practice conclusions may need to be drawn acknowledging that at the time of the assessment some of these questions remain unanswered.

7.1.2.1. Integrated questions for risk assessment of causation between prenatal exposure and adverse pregnancy outcomes

1. **Exposure Timing:** Was there documented exposure to the medicinal product at critical times during prenatal development, and does the exposure precede the observed adverse pregnancy outcomes? Is there (animal) data on placental transfer?
2. **Consistent Findings:** Are there consistent findings by multiple epidemiological studies of adequate quality showing a relationship between exposure and adverse pregnancy outcomes? Do other data sources provide further support for concern?
3. **Strength of Association**: What is the magnitude of the observed association between exposure and adverse pregnancy outcomes as indicated by clinical studies (for a non-interventional study, consider the degree of potential residual confounding)? What is the precision of the estimated association?
4. **Specificity of Clinical Phenotype**: Is there a specific pattern of defects reported after the exposure? An embryo/fetotoxic substance rarely causes congenital malformations in a wide range of organs. A specific pattern of congenital malformations generally increases the likelihood of a causal relationship.
5. **Biological Mechanism**: Does the association make biological sense, supported by evidence of a plausible biological mechanism of action, from non-clinical and / or clinical data?
6. **Class effects (i.e. analogy):** Have similar medicinal products shown similar adverse outcomes, pointing to a class effect that supports a causal relationship, based on non-clinical and / or clinical data?
7. **Dose-Response:** Is there evidence of a dose-response relationship, indicating that higher exposure levels are associated with greater risks of adverse outcomes?
8. **Non-clinical Evidence**: Is there evidence of adverse embryo-fetal effects in toxicity studies supporting causality between exposure and adverse pregnancy outcomes? Is the substance genotoxic?
9. **Integration and Coherence:** Does the overall body of evidence support a coherent and consistent conclusion about a causal relationship between the exposure and adverse pregnancy outcomes?

7.1.2.2. Identified risk for adverse pregnancy outcomes

The evidence supporting an identified risk may include:

- Study(ies) in humans, with designs and results of sufficient quality to conclude on causality, consistently suggesting an increase in the overall frequency of an adverse pregnancy outcome (or a specific type of an adverse pregnancy outcome). Factors that may be considered include the strength of the association of exposure to the medicinal product *in utero* with the adverse pregnancy outcome, any evidence of a dose-response relationship, and coherence of the overall body of evidence, as described in the questions in section 7.1.2.1 above.
- Several relevant case-reports, where assessment conclude that a causal relationship between the medicinal product and the adverse pregnancy outcome is at least a reasonable possibility. Factors supporting such relationship include known exposure during the critical period, low frequency of the adverse pregnancy outcome in the general population, specific effect (e.g. an unusual pattern of an adverse pregnancy outcome), plausible mechanism for the adverse pregnancy outcome in relation to the mechanism of action, known association of other medicinal products in the same class with the adverse pregnancy outcome, and consistency with non-clinical findings of a harmful effect of exposure to the medicinal product in pregnancy.
- Non-clinical data which show a harmful effect(s) after exposure to the medicinal product during gestation, with suspected relevance to humans and with insufficient clinical data;

- Mechanism of action with evidence of being a risk for adverse pregnancy outcomes, including known class effects.

7.1.2.3. Potential risk for adverse pregnancy outcomes

The evidence supporting a potential risk may include:

- Non-clinical data which raise concerns for a harmful effect(s) due to exposure to the medicinal product during gestation, with possible relevance to humans but with insufficient clinical data.
- Mechanism of action which is suspected to adversely interfere with development. This includes possible class effects of risk for adverse pregnancy outcome(s).

and/or

- Studies or sources of data such as analysis of human case reports suggesting an increase in the overall frequency of the adverse pregnancy outcome, but insufficient evidence to conclude on causality, due to limitations, inconsistency of findings across data sources, or a lack of other studies or data to corroborate the findings of a single data source. This includes the relevance of the methodology and results of each study and source of data.

7.1.2.4. Adverse effects unlikely in humans

When a sufficiently large amount of clinical data of adequate quality is available, not raising concerns for adverse pregnancy outcomes, and when knowledge regarding the pharmacological effects of the substance does not raise such concern, it can be concluded that adverse pregnancy effects are unlikely. This would generally correspond to several thousand pregnancies, well documented within a relevant study setting. In this situation, beyond pharmacological data, the non-clinical data have less importance for risk assessment. For some formulations, pharmacokinetic data in humans, showing very low systemic exposure can also support risk assessment.

7.1.2.5. Insufficient data with respect to pregnancy

For substances where non-clinical data, including knowledge of pharmacological effects, do not raise concerns, but where clinical data are limited, and therefore no firm reassuring conclusions can be drawn. In these situations, available data are considered insufficient.

7.1.3. Breastfeeding

Following the integrated assessment outlined in section 6, a general risk classification can be applied, based on the available evidence and its strengths and limitations. In all situations below, if the medicinal product is not absorbed from the infant's gastrointestinal tract, it will not cause systemic effects, but it can still cause local effects in the gastrointestinal tract, such as diarrhoea.

7.1.3.1. Identified risk for breastfed infants

The evidence supporting an identified risk may include:

- Adverse reactions in breastfed infants in line with the known safety profile and/or the pharmacodynamic effects of the substance.
- Clinically relevant systemic exposure of breastfed infants to the active substance (and/or its metabolites), and/or if the substance (and/or metabolites) is present in significant amounts in breast milk can also support concluding on an identified risk for breastfed infants.

7.1.3.2. Potential risk for breastfed infants

The evidence supporting a potential risk may include:

- Safety profile of a medicinal product including relevant risks, taking pharmacodynamic properties as well as class effects into account, but data on transfer into breastmilk or data on exposure of breastfed infants are lacking. This assessment can in some instances be based on non-clinical data solely, particularly from toxicity testing including peri- and post-natal or juvenile toxicity studies.
- Limited data on milk transfer or of infant exposure suggest levels of the active substance, that may cause adverse effects in the infant.
- Data on milk transfer or infant exposure is not available or limited, but physicochemical properties of active substance, data from a qualified physiologically based pharmacokinetic model using scarce human samples, or from a qualified *in vitro* method, point to possible high transfer into breast milk.

7.1.3.3. Adverse effects unlikely in breastfed infants

The evidence supporting that adverse effects are unlikely in breastfed infant may include:

- Sufficient human data from the use in breastfeeding individuals not suggesting a risk, including no reported adverse reactions in the infant.
- Robust data showing that the levels of the substance/metabolites in breastmilk are so low (see section 8.2.1.2) that they are unlikely to pose a concern to the breastfed infant. Alternatively, data may show that the medicinal product does not enter breast milk and/or is not absorbed systemically by the infant.

7.1.3.4. Insufficient data with respect to breastfeeding

When clinical data from breastfed infants, or on levels in breastmilk are absent or limited, data are considered insufficient. The overall safety profile of the substance does not raise serious concerns.

7.2. Principles for recommendations

7.2.1. Fertility

In most cases, recommendations are not provided in the PI in relation to data on fertility. However, on a case-by-case basis, it may be warranted to include a recommendation into the PI, taking the following into account (see section 8.2.1.3):

- In case of an identified risk of temporarily impaired fertility, a recommendation not to use the medicinal product in males and/or females attempting to conceive, can be considered. Further, in individuals with difficulties conceiving or who are undergoing investigation of infertility, a recommendation to withdraw the treatment can be considered.
- If a risk of irreversible damage of male and/or female gametes has been identified, inclusion of a recommendation seeking counselling for sperm or oocyte preservation before starting treatment, can be considered.

7.2.2. Pregnancy

The potential risks of *in utero* exposure to the medicinal product for the developing embryo or fetus (see section 7.1.2), the potential benefits of treatment for the pregnant individual, the risks the untreated condition may pose to both, and alternative treatments, should be taken into account when determining the recommendation for use of the medicinal product in pregnancy. These recommendations should be based on available information from:

- Clinical experience
- Relevant non-clinical studies

- Need for treatment

7.2.2.1. Clinical experience

In case of a potential or an identified risk for serious adverse pregnancy outcomes such as major congenital malformations or NDD (see section 7.1.2), a contraindication to use of the medicinal product in pregnancy, or during defined parts of pregnancy should be considered.

A contraindication should also be considered if the medicinal product has a pharmacological profile (mechanism of action) similar to that of a substance or therapeutic class where serious adverse pregnancy outcomes are an identified risk in humans.

In cases when available non-clinical and clinical evidence suggests a lower concern for serious adverse pregnancy outcomes, less strict recommendations should be given, taking the need for treatment into account (see section 7.2.2.3).

7.2.2.2. Relevant non-clinical studies

In some circumstances, a contraindication in humans may be based on non-clinical data only, after a comprehensive assessment of all relevant aspects, such as:

- Pharmacology/mechanism of action: properties known to cause direct or indirect embryo-fetal damage
- Genotoxic potential
- EFD: lethality, congenital malformations, embryo-fetal toxicity including growth retardation, and functional changes, taking the severity of the observed findings, and the exposure level in relation to the human therapeutic exposure into account.

7.2.2.3. Need for treatment

Where the assessment concludes on an identified or potential risk for adverse pregnancy outcomes, such risk has to be weighed against the potential benefit of the treatment for the pregnant individual, before a recommendation is concluded upon. The following points should be taken into consideration:

- Serious or life-threatening disease, as well as the impact of pregnancy on the disease and the impact of the disease on pregnancy.
- An alternative treatment option, with relevant therapeutic benefit, is available that is safer when used in pregnancy.
- Treatment can be modified, postponed or avoided.

A contraindication in pregnancy should only be considered if either, a) safer alternative treatment option is available or, b) treatment can be postponed until after pregnancy.

If there is no safer treatment option available and treatment cannot be delayed, the medicinal product should generally not be contraindicated in pregnancy. However, strict recommendations against use in pregnancy and actions to take in case of pregnancy occurring, or if pregnancy is being planned while on treatment, should be included in the SmPC and PL. See also section 8.2.1.

7.2.2.4. Recommendations for use during pregnancy

Recommendations for use in pregnancy should be based on all relevant evidence, and take the risk classification described in section 7.1.2 into account:

- **Medicinal product is contraindicated during pregnancy** – This applies when an identified or potential risk for serious adverse pregnancy outcome(s) has been concluded upon, and when treatment can be postponed until after pregnancy, or the medical condition can be managed by an alternative treatment option.
- **Medicinal product should not be used during pregnancy unless the medical condition requires treatment with {active substance} and cannot be managed by an alternative treatment** – This applies when an identified or potential risk for a serious adverse pregnancy outcome(s) is concluded upon, and treatment cannot be postponed until after pregnancy or the medical condition cannot be managed by an alternative treatment option. This also applies when available data are insufficient to draw conclusions about the risk of *in utero* exposure, but available evidence raises concerns for adverse pregnancy outcomes. This advice can be adapted to meet specific exposure windows when adequately justified.
- **Use of the medicinal product may be considered during pregnancy** – This applies when data are limited but available evidence does not raise concerns for serious pregnancy outcomes.
- **Medicinal product can be used during pregnancy** – This applies when the risk assessment of available evidence concludes on an unlikely risk.

7.2.3. Individuals of reproductive potential

The need for a recommendation for females of reproductive potential to use effective contraception [8,23] to prevent unplanned pregnancy during treatment should be considered when a medicinal product has an identified or potential risk for adverse pregnancy outcomes.

Factors that should be taken into account include the robustness of available evidence, the magnitude and severity of identified or potential risk, the target population, and availability of alternative treatment options. Recommendations for females of reproductive potential will also depend on the recommendation with respect to use of the medicinal product in pregnancy.

In exceptional cases, for an active substance which can cause serious adverse pregnancy outcomes in human, there can be concerns that the substance can affect embryo-fetal development through transfer to a pregnant individual via seminal fluid from a male individual being treated with the substance [8]. In such situation, a recommendation for male individuals to use a condom if engaged in sexual activity with a pregnant individual or a female of reproductive potential not using effective contraception may be considered.

7.2.3.1. Recommendations for use in females of reproductive potential

Where the medicinal product is contraindicated in pregnancy (see 7.2.2.4):

- In exceptional circumstances, if a risk of serious embryo-fetal or neonatal harm of larger absolute magnitude has been concluded, the need to prevent exposure to the medicinal product in pregnancy by contraindicating use in females of reproductive potential, unless they are using effective contraception, should be considered.
- In most situations, such contraindication is not warranted. Instead, a recommendation that the medicinal product should not be used in females of reproductive potential unless they are using effective contraception is sufficient.
- In some situations, depending on the indication and the context for use e.g. acute treatments, a recommendation to use effective contraception in females of reproductive potential is not warranted.

Where the medicinal product should not be used during pregnancy unless the medical condition requires treatment with the active substance and cannot be managed by an alternative treatment (see 7.2.2.4):

- When an identified or potential risk for a serious adverse pregnancy outcome(s) is concluded upon, or when available data are insufficient to draw conclusions, but available evidence raises concerns for adverse pregnancy outcomes, a recommendation that females of reproductive potential should use effective contraception should be considered, depending on the potential safety concerns.

For all the above situations, there may be circumstances where the possibility for becoming pregnant is very low for a female of reproductive potential. In these circumstances an effective contraception may not be necessary, following discussion with the prescriber. Where such circumstances may change, this should be reviewed regularly.

7.2.3.2. Recommendations on risk minimisation measures

When the assessment has concluded on an identified risk or a potential risk of serious adverse pregnancy outcomes, concrete measures to avoid or minimise exposure to the medicinal product during pregnancy should be provided in the PI (see section 8 and Annex).

Actions to ensure adherence to recommendations in the PI can be combined with additional tools of risk minimisation, including, in exceptional cases, a pregnancy prevention programme (See GVP Module XVI Addendum I – Risk minimisation measures for medicinal products with embryo-fetal risks [24]).

7.2.4. Breastfeeding

Recommendations for use during breastfeeding should be based on all relevant evidence, including the known benefits of breastfeeding, and take the risk classification described in section 7.1.3 into account.

7.2.4.1. Considerations for recommendations in breastfeeding

A medicinal product should only be contraindicated during breastfeeding if there exists an identified or potential risk of serious adverse reaction(s) in the breastfed infant. In some circumstances, a potential serious risk can be based on non-clinical or indirect evidence only. Absence of relevant data on breastfeeding alone is not a sufficient reason for a contraindication. The reasons for the (potential or identified) serious risk should be described. If there is concern about a possibility of a potential serious risk for the infant, a recommendation that the medicinal product should not be used during breastfeeding is warranted.

If there is a concern about an identified or potential non-serious risk for the infant, a cautionary warning about the use of the medicinal product during breastfeeding should be included, with an explanation provided. This can include that use of the medicinal product during breastfeeding may be considered, with a recommendation to closely observe the breastfed infant (indicating which adverse reactions could be expected) to determine when discontinuation or an interruption of breastfeeding becomes necessary. Alternatively, recommendations on temporary interruption of breastfeeding should be provided, if this is a feasible alternative instead of recommending stopping breastfeeding. In such cases, the duration of interruption should be stated, and the time interval should be estimated based on the half-life of the active substance (and/or active metabolites), oral bioavailability, and safety profile. As a general rule, active substance (and/or metabolites) levels in breast milk are considered negligible after approximately five elimination half-lives [25].

7.2.4.2. Recommendations for use during breastfeeding

Recommendations for use during breastfeeding should be based on all relevant evidence, and take the risk classification described in section 7.1.3 into account:

- **Medicinal product is contraindicated during breastfeeding**– this applies in case of an identified serious risk or a potential serious risk for the breastfed infant.
- **Medicinal product should not be used during breastfeeding**– this applies when serious risk for breastfed infant has not been demonstrated but is a possibility.
- **Medicinal product may be considered during breastfeeding–** this applies when data are limited but available evidence does not raise concerns for serious risk. This includes infant exposure being unknown or may potentially lead to adverse effects, although a serious risk is not expected.
- **Medicinal product can be used during breastfeeding**– this applies when the risk assessment of available evidence concludes on an unlikely risk.

8. Reflections for the product information

8.1. Introduction

In the SmPC and PL, information regarding male and female fertility, pregnancy and breastfeeding should include different elements namely:

- Recommendations with respect to use of the medicinal product in these different populations, as appropriate.
- A concise summary of available data concerning use of the medicinal product in these different populations, including potential and identified risks, impact on relevant outcomes and areas of uncertainty.
- Details of recommended actions for risk minimisation to prevent or minimise exposure during pregnancy, or during breastfeeding, as appropriate, and / or recommendations for females of reproductive potential, or in some cases, in relation to male fertility.

The overall aim of the wording in the PI is to enable informed and shared decision-making by healthcare professionals and patients (or individuals and facilitate adherence to risk minimisation measures.

8.2. Summary of product characteristics (SmPC)

In section 4.6 *Fertility, pregnancy and lactation*, information and recommendations regarding use in pregnancy, and breastfeeding, as well as information regarding fertility should always be included.

In some cases, other sections, e.g. section 4.3 *Contraindications*, 4.4 *Warnings and precaution*s, 4.5 *Interactions* and section 4.8 *Undesirable effects* may also complement section 4.6.

Relevant pharmacokinetic data should be reflected in section 5.2 and non-clinical data should be reflected in section 5.3, including addressing reproductive and developmental effects. In all relevant cases, cross-references between sections should be added.

If additional risk minimisation tools are implemented (e.g. educational materials for health care professionals and/or patients), these should generally be referred to in section 4.4 or 4.6 of the SmPC, and in section 2 of the PL.

8.2.1. Section 4.6 of the SmPC

8.2.1.1. Subsection on pregnancy and females of reproductive potential

Clinical data:

Describe the extent of human experience and from which data sources (see sections 5.3 and 7.1.2). When at least a few hundred prospectively observed exposed pregnancies with known outcomes are available, it is generally appropriate to detail the numbers of pregnancies, particularly when there are data from relevant clinical studies (clinical trials or pharmacoepidemiological studies). Where the number of exposed pregnancies with known outcomes is small (generally less than 100), a more general description of the data, e.g. being 'limited' is more suitable, to reflect data limitations. It will also avoid small specific numbers becoming rapidly outdated.

If data are sufficiently robust, e.g. results from clinical trials or pharmacoepidemiological studies of adequate size and quality, the knowledge on main adverse pregnancy outcomes should be summarised. In case there is a reasonable possibility for a causal relationship between an adverse pregnancy outcome and exposure, describe:

- Primary sources of evidence for the observed risk, including (where available) details on pregnancy exposure (timing, duration), the magnitude of the risk (relative, absolute, and background frequencies), and the nature of the risk (such as patterns of congenital malformations or NDD and their severity). Include the comparator used in relevant studies, if applicable.
- Relevant areas of uncertainty regarding adverse pregnancy outcomes. This may in some circumstances relate to studies with different results, leading to the overall picture being inconclusive.

Also, when adequate clinical data provide reassurance regarding use in pregnancy, the primary sources of evidence, including details on pregnancy exposure (timing, duration), main pregnancy outcomes, and the comparator used if applicable, should be described. If some uncertainties remain, those should be summarised shortly.

Non-clinical data:

Only general conclusions of the non-clinical evaluation should be included in section 4.6 of the SmPC. Further details should be provided in section 5.3 of the SmPC.

Recommendations:

As detailed in sections 7.2.2. and 7.2.3., a recommendation should be included, which generally ranges from a contraindication in pregnancy and in females of reproductive potential not using effective contraception, to can be used in pregnancy.

In case measures to minimise or avoid exposure during pregnancy are warranted, those should be described (see GVP Module XVI Addendum I [24] for further details), including:

- **Risk counselling** including the potential risks of using the medicinal product during pregnancy and the recommendations regarding use during pregnancy.
- **Pregnancy testing** to ensure excluding pregnancy before initiating treatment with the medicinal product (and in exceptional situations during and after treatment discontinuation). Pregnancy testing would generally be included in the PI as a risk minimisation measure when use in pregnancy is contraindicated.
- When **effective contraception** is recommended, the exact type of contraceptive method should not be defined, since selection of a contraceptive method should be evaluated individually by the prescriber and person to be treated. However, in some instances, a medicinal product may impair

the effectiveness of some methods of contraception. Such data should be described in the product information (e.g. section 4.5) and may lead to recommendations on type of contraceptive methods. Based on the pharmacokinetic properties of the medicinal products, duration of contraceptive use after stopping treatment should be included in the PI.

- **Actions if a patient considers a pregnancy** during treatment or in the event of an **unplanned pregnancy** during treatment with the medicinal product. This includes promptly contacting a healthcare professional to consider the possibility of e.g. interrupting treatment, dose reduction, switching to an alternative treatment and/ or relevant specific monitoring during pregnancy such as fetal ultrasound or of the neonate/infant.
- Consideration to add advice that treatment should be supervised by a physician who is experienced in the management of the medical condition and the use of the medicinal product, and on regular medication reviews.
- Where relevant, consider advice to deter patients from donating blood during and for a specified period after use of the medicinal product, and/or to deter patients from donating semen during and for a specified period after use of the medicinal product.

8.2.1.2. Subsection on breastfeeding

All relevant data which are the basis for the recommendation should be shortly described (see also sections 7.1.3 and 7.2.4). This includes conclusions of pharmacokinetic studies e.g. plasma concentrations in breastfed infants, concentrations of the active substance and/or its metabolite(s) in human breast milk (including if it is unknown), calculated relative or daily infant dose. If non-clinical data are part of the basis for the recommendation, these should be shortly summarised, with reference to section 5.3 for further details. Estimated absorption from an infant´s gastrointestinal tract should be reported if relevant.

If possible, quantify the extent of transfer into breastmilk using relative infant dose categories (<2% minimal, 2–5% low, 5–10% moderate, >10% high) [25] and specify relevant details such as route of administration and/or dosage strength. If known, the amount relative to a therapeutic infant dose and infant plasma/blood levels could be mentioned.

Information on known risks in breastfed infants, or long-term clinical experience without observed risks of specific serious concern, should be included if available.

Other important information should be mentioned, such as large size of molecules possibly precluding breast milk transfer, lack of oral bioavailability, reminder of safety profile, among others.

The SmPC should describe, when applicable, measures that are intended to minimise exposure of the breastfed child to the medicinal product and/or its active metabolite(s), such as timing the administration of the medicinal product relative to breastfeeding and/or short-term interruption of breastfeeding.

8.2.1.3. Subsection on fertility

The SmPC should describe potential impacts on fertility whenever available evidence indicates that the medicinal product may impair fertility, including whether temporary or irreversible effects.

Main information on the possible effects of the medicinal product on fertility should be included:

- Clinical data if available.
- Relevant conclusions from non-clinical toxicity studies if available. Further details should be included in Section 5.3 of the SmPC.

On a case-by-case basis (see sections 7.1.1 and 7.2.1), it may also be warranted to include advice on practical considerations e.g., avoiding use in the context of assisted reproductive technology treatment, for individuals with difficulties conceiving or who are undergoing investigation of infertility, counselling for gamete preservation or advice not to donate gametes.

Cross-references could be included to other relevant sections of the PI (e.g. section 4.4 of the SmPC), if appropriate.

8.2.2. Section 4.3 of the SmPC

- Contraindication in pregnancy (see section 7.2.2.4), or defined parts of pregnancy, with cross-references to section 4.4 (if considered appropriate) and section 4.6 where further information about the background to the contraindication as well as all risk minimisation measures should be provided.
- Contraindication in females of reproductive potential (see section 7.2.3.1) unless they are using effective contraception, with cross-references to section 4.4, if considered appropriate and to section 4.6 where further information about the background to the contraindication should be provided.
- Contraindication in breastfeeding (see section 7.2.4.2), with cross-references to section 4.6 where reasons for contraindication should be explained.

8.2.3. Section 4.4 of the SmPC

If a medicinal product is contraindicated in pregnancy and/ or in females of reproductive potential, including if a pregnancy prevention programme is implemented (see GVP Module XVI Addendum I [24]), section 4.4 may shortly state the key risk(s) justifying a contraindication, and shortly focus on key measures to minimise risk, including pregnancy testing before treatment initiation and use of contraception, with cross-reference to section 4.3, 4.5 (if applicable) and 4.6, where further details on the risk as well as on risk minimisation measures should be described.

8.2.4. Section 4.5 of the SmPC

If contraceptive measures are recommended for females of reproductive potential (see section 7.2.3), relevant information concerning interactions of the medicinal product with methods of contraception should be addressed, with cross-references to e.g. sections 4.3, 4.4, 4.6 and 5.2.

8.3. Package leaflet (PL)

The package leaflet should reflect all relevant information from the SmPC, and be written in a comprehensible, lay-person friendly language.

Section 2

Contraindications and precautions for use or special warnings should be included in Section 2 of the PL.

Under Do not take [X]:

- Contraindication if the patient (or individual) is pregnant (if considered appropriate)
- Contraindication if the patient (or individual) is a female able to have a child (if considered appropriate) unless using effective birth control.
- Contraindication if the patient (or individual) is breastfeeding (if considered appropriate)

Under Pregnancy, breastfeeding and fertility:

- Contraindications or recommendations with respect to use of the medicinal product in pregnant patients (or individuals), during breastfeeding or in female patients (or individuals who can have a child.
- Information on the risks following exposure to the medicinal product in pregnancy, including (where available):
  - The type of adverse pregnancy outcome, e.g., the pattern of congenital malformations or the specific type of NDD associated with use of the medicinal product during pregnancy, including severity.
  - The magnitude of the risk(s) preferably described in absolute terms and in relation to a relevant comparator. For instance, expressing the number of babies being affected by the adverse effect among every 100 babies born to individuals taking the medicinal product, compared with the same figures for babies born to individuals not taking the medicinal product or for babies born of individuals who do not have the indication for the medicinal product (as appropriate).
- If available, information in relation to dose or duration of use.
- Lack of evidence, and/or reassuring findings, if appropriate.
- Information on actions to take to prevent exposure to the medicinal product during pregnancy, during breastfeeding and in an individual who can have a child, in line with recommendations in the SmPC. Examples on actions to take can be given in the PL as aid to the individual.
- Information on actions if pregnancy occurs or is considered during treatment, as appropriate, in line with recommendations in the SmPC.
- Information on the possible effects following exposure to the medicinal product on male and female fertility.

9. References

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2. ICH S5 (R3) Guideline on detection of reproductive and developmental toxicity for human pharmaceuticals (EMA/CHMP/ICH/544278/1998)
3. ICH S3A Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies (CPMP/ICH/384/95 (ICH S3A)).
4. ICH M3(R2) Guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)
5. ICH M3 (R2) - questions and answers (EMA/CHMP/ICH/507008/2011)
6. Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)
7. ICH S2 (R1) Guideline on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (Step 5. 2013) (EMA/CHMP/ICH/126642/2008)
8. Safety Working Party (SWP) / Non-clinical Working Party (NcWP) recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020)
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10. Guideline on good pharmacovigilance practices (GVP): Product- or population-specific considerations III: Pregnant and breastfeeding women and their children exposed in utero or via breastmilk (EMA/653036/2019)
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15. Birth Defects Prevalence — U.S. National Estimates, 2018–2022. Centers for Disease Control and Prevention (CDC), Available at https://www.cdc.gov/birth-defects/media/pdfs/2026/04/Data-Brief-Birth-Defects-National-Estimates-2018-2022.pdf
16. ICD-11 for Mortality and Morbidity Statistics. WHO, Available at https://icd.who.int/browse/2024-01/mms/en#1516623224
17. ICH S6 (R1) Guideline on Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998 (ICH S6)
18. EMA Reflection paper on non-human primates in safety testing of human medicinal products and opportunities for 3Rs implementation (EMA/CHMP/55697/2025)
19. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) (EMA/838713/2011)

20. Rasmussen S, Jamieson D, Honein M, Petersen L. Zika Virus and Birth Defects — Reviewing the Evidence for Causality. N Engl J Med 2016;374:1981-1987
21. Shepard TH. "Proof" of human teratogenicity. Teratology 1994; 50: 97-8.
22. Frank C, Faber M, Stark K. Causal or not: applying the Bradford Hill aspects of evidence to the association between Zika virus and microcephaly. EMBO Mol Med 2016 March 1
23. Recommendations related to contraception and pregnancy testing in clinical trials, CTCG Clinical Trials Coordination Group
24. Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum I – Risk minimisation measures for medicinal products with embryo-fetal risks (EMA/608947/2021)
25. Hale's Medications & Mothers' Milk 2025-2026: A Manual of Lactational Pharmacology 21st ed. Edition by Thomas W Hale Rph PhD (Author), Kaytlin Krutsch PhD Pharmd MBA Bcps (Author)

Annex

Standard statements for section 4.6 of Summary of Product Characteristics (SmPC) and section 2 of Package Leaflet (PL):

There are three tables with statements for the SmPC and the PL:

- Table 1 - Pregnancy and Females of reproductive potential
- Table 2 – Breastfeeding
- Table 3 - Fertility.

Tables 1 and 2 are divided into sections for each recommendation of use, ranging from a strict contraindication to that the medicinal product can be used. For each recommendation in table 1 and 2, there are different statements to be used in describing available data and risk minimisation measures, if applicable, or other relevant information for the medicinal product, based on the specific assessment (see sections 7 and 8). For fertility, standard statements to describe data are provided, since in most cases, specific recommendations are not provided in the product information in relation to fertility. Recommendations may be needed on a case-by-case basis, specifically in situations of identified risk of temporarily impaired fertility, difficulties conceiving or risk of irreversible damage in fertility (see table 3 and section 7.2.1).

The structure of the product information should be in accordance with the QRD template, i.e. pregnancy, breastfeeding and fertility, with additional sub-headings in the SmPC and PL, such as "Women of childbearing potential", "Contraception in males" or "Contraception in females", as appropriate. Furthermore, in the QRD template, each subsection starts with description of data, followed by a recommendation and risk minimisation measures, if applicable.

How to compile the standard statements

SmPC

The assessment of available data for a specific medicinal product, will result in a Recommendation (Section 7.2). This recommendation will be the starting point for compiling a complete wording for each subpart of section 4.6 of the SmPC. In general, standard wording should be selected from one of the recommendations only, although it can be adapted if there are no suitable wording for a specific case.

To compile the standard statement, begin with the text in the recommendation-box for the applicable recommendation, and continue adding text following the steps under the appropriate recommendation (e.g. female of reproductive potential, data description, risk minimisation measures) and include the

standard statement that is suitable for the intended medicinal product. If a subsection is irrelevant for the intended medicinal product (e.g. risk minimisation measures), no standard statement should be included from that specific subsection.

Package leaflet

When compiling the information for the section 2 of the Package leaflet, use the corresponding text in relation to the standard statements used for the SmPC. In some cases, there are more options in the PL compared to the SmPC standard statements. In such case, use one or several of the PL standard statements, considering the relevance of the intended product. It is also acceptable to change the order of the selected standard statements, compared to the order in this Annex, to get a readable text without repetition of information.

Note: {active substance}: there may be cases for which it is most appropriate to use {invented name} i.e.: when the risk depends on the route of administration or the formulation; N/A – Not applicable. Information is not relevant for the individual (e.g. lack or uncertainty of clinical data, non-clinical data). No statement should be included in the package leaflet.

Table 1. Pregnancy and females of reproductive potential

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	<u>Recommendation 1:</u> The medicinal product is contraindicated during pregnancy	
	[Section 4.3] Pregnancy <{trimester} of pregnancy> (see section 4.6) *[Section 4.6] Treatment with {Active substance} is contraindicated during <pregnancy><the {number} trimester of pregnancy> and<up to {number} weeks <after><before> pregnancy> (see section 4.3).*	*[Pregnancy] Do not <take><use> this medicine <if you are pregnant><during the <first><last> <3 months><6 months> of pregnancy> and <up to {number} weeks <after><before> pregnancy> because it can harm the child.*
Step 1. Select recommendation for female of reproductive potential (select one of two options as appropriate to the product and its indication)		
Option 1	*[Section 4.3]* Females of reproductive potential, unless they are using effective contraception.	*[Pregnancy]* Do not <take> <use> this medicine if you can become pregnant, unless you are using effective birth control.
	[Section 4.6 <section 4.4>] Females of reproductive potential must use effective contraception during treatment with {active substance} and < for {number <days><weeks><months>}> after treatment>.	*[Pregnancy]* If you can become pregnant, you must use effective birth control during treatment with this medicine <and for <at least> {number < days >< weeks><months>} after the last dose of this medicine>. You must not become pregnant while <taking><using> this medicine.

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	[Section 4.6 <section 4.4>] Individual circumstances should be evaluated together with the patient when choosing the contraceptive method. There may be individual circumstances where a female is not required to use effective contraception during <and after> treatment with {active substance} following discussion with their prescriber. This should be regularly evaluated to determine whether circumstances change.	*[Pregnancy]* Talk to your doctor about birth control methods that may be right for you. Your doctor will give you information on preventing pregnancy and may refer you to a specialist for advice on birth control.
Option 2	*[Section 4.6]* In females of reproductive potential, effective contraception during treatment with {active substance} <and < for {<number> < days >< weeks><months>}> after treatment> is recommended.>	*[Pregnancy]* If you can become pregnant, effective birth control during treatment with this medicine <and for <at least> {<number> < days >< weeks><months>} after the last dose of this medicine> is recommended.
	[Section 4.6] Individual circumstances should be evaluated together with the patient when choosing the contraceptive method.	*[Pregnancy]* Talk to your doctor about birth control methods that may be right for you. Your doctor may refer you to a specialist for advice on birth control.
Step 2. Select most suitable text describing available data relevant for pregnancy		
Clinical data **Option 1**	*[Section 4.6]* Data from {type of study}, including approximately {number} pregnancies, exposed during {Y trimester}, <show > <suggest > an approximately {number}-fold increase in {main adverse pregnancy outcome(s)} corresponding to {concrete data/numbers; excess risk estimates (if possible); pattern of {main adverse pregnancy outcome(s)} observed; existence of dose-related effects}, compared with {reference/comparator group, confidence intervals and background frequency, as applicable}.	*[Pregnancy]* This medicine may <in <very> rare cases> increase the risk of <birth defects <such as {list the side effects}><{main adverse pregnancy outcome(s)}> when taken during pregnancy. *[Pregnancy]* <In pregnant individuals who take {active substance}, around {number or number interval} children in every {number} will have birth defects. This compares with {number or number interval} children in every {number} born to individuals who do not have {condition} and do not take a {medicine class} treatment.>
Option 2	*[Section 4.6]* Based on <human experience {describe type of experience shortly}> <and> <or> <mechanism of action>, {active substance} <increases> <may increase> the risk of embryo-fetal harm when administered during pregnancy.	
Option 3	*[Section 4.6]* There are no or limited data from the use of {active substance} in pregnant individuals.	N/A

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
Non-clinical data **Option 1**	*[Section 4.6]* Non-clinical data have shown developmental toxicity, including <malformations><embryo-fetal lethality><peri/postnatal mortality> (see section 5.3).	N/A
Option 2	[*Section 4.6]* Based on non-clinical data <from developmental toxicity studies and/or mechanism of action> (see section 5.3) {active substance} <increases> <may increase> the risk for embryo-fetal harm when administered during pregnancy.	
Option 3	*[Section 4.6]* Non-clinical data are insufficient with respect to developmental toxicity (see section 5.3).	
Step 3. Select further risk minimisation measures (<> bracket indicates to select as appropriate to the product, risk and indication) *The alternatives below concern cases where the product is contraindicated in pregnancy and in females of reproductive potential unless they are using effective contraception, or where the product is contraindicated in pregnancy but not in females of reproductive potential*		
	[Section 4.6] <Educational materials for risk minimisation measures <select relevant material e.g. checklist, guide> are available for <health care professional> <patients > <and caregivers>. The patient <select additional risk minimisation material e.g. patient guide or patient card> must be provided to <select target group e.g. females of reproductive potential >.	*[Pregnancy]* <Read the <select additional risk minimisation material e.g. patient guide, patient card> <that you will receive from your <doctor><pharmacist> <find in the package> >
<Pregnancy testing>	*[Section 4.6 <section 4.4>]* In females of reproductive potential, a pregnancy test must be negative before the start of treatment with {active substance}.	*[Pregnancy]* If you can become pregnant, you must take a pregnancy test that must be negative before starting treatment with this medicine.
<Counselling >	*[Section 4.6 <section 4.4>]* Females of reproductive potential must be advised about the risks of using {active substance} during pregnancy and about the risk minimisation measures to avoid use during pregnancy, including contraceptive measures.	*[Pregnancy]* Talk to your doctor about the risks of <taking><using> this medicine during pregnancy for advice on <appropriate actions to avoid becoming pregnant><and><or><birth control methods >, if you can become pregnant.
<When pregnancy is considered during treatment>	*[Section 4.6 <section 4.4>]* If a female using {active substance} plans to become pregnant, treatment must be discontinued <, and, if needed, switched to an alternative treatment> before contraception is discontinued. To facilitate this,	*[Pregnancy]* If you are planning to become pregnant during the use of this medicine, treatment with this medicine must be stopped<, and, if needed, switch to another medicine> before stopping birth control. <Your doctor will discuss with you your treatment needs and suitable treatment alternatives.>Do not stop <taking><using> your birth control before you have discussed it with your doctor.

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	-<the female should be advised to consult her physician as soon as she is planning pregnancy>. -<a specialist experienced in the management of {the indication for the product} must be consulted>.	*[Pregnancy]* <Talk to your doctor <or to a specialist experienced in {the indication for the product}> as soon as you plan to become pregnant during treatment with this medicine.>
<Unplanned pregnancy during treatment>	*[Section 4.6 <section 4.4>]* If an individual becomes pregnant while using {active substance}: -<the individual should be advised to urgently consult the physician>. -<the individual should be advised to immediately cease treatment with {active substance}.> -<the individual must be immediately referred to a specialist to re-evaluate treatment with {active substance} and consider alternative options>. The individual should be evaluated and counselled regarding the exposed pregnancy.	[Pregnancy] If you discover that you are pregnant while <taking><using> this medicine, - <talk to your doctor immediately for advice. Do not delay seeking medical guidance.> - <do not stop <taking><using> this medicine on your own, as your condition may become worse.> - <your doctor can tell you to stop treatment immediately> - <your doctor will urgently refer you to a specialist experienced in treating {the indication for the product}. The specialist will reassess your treatment and consider another medicine for you.> - <you may also get advice about the possible effects of this medicine on your pregnancy and your treatment options.>
<u>Recommendation 2:</u> Medicinal product should not be used during pregnancy unless medical condition requires treatment and cannot be managed by an alternative treatment.		
	[Section 4.6] {Active substance} should not be used during <pregnancy>< the {number} trimester><up to {number} weeks <after><before> treatment> unless the medical condition requires treatment with {active substance} and cannot be managed by an alternative treatment.	*[Pregnancy]* You should not <take><use> this medicine <if you are pregnant><during the {number} trimester of pregnancy><up to {number} weeks <after><before> treatment> unless considered necessary for treating your condition, and any other treatment is not suitable.
Step 1. Select recommendation for female of reproductive potential (select one of two options as appropriate to the product and its indication)		
Option 1	*[Section 4.6]* In females of reproductive potential, effective contraception should be used during treatment with {active substance} and <for {number} < days >< weeks><months>><after treatment>>	*[Pregnancy]* If you can become pregnant, effective birth control during treatment with this medicine <and for <at least> {<number> <days >< weeks><months>} after the last dose of this medicine> is recommended.

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	[Section 4.6] Individual circumstances should be evaluated together with the patient when choosing the contraceptive method.	*[Pregnancy]* Talk to your doctor about birth control methods that may be right for you. Your doctor will give you information on preventing pregnancy and may refer you to a specialist for advice on birth control.
Option 2	*[Section 4.6] No recommendation for females of reproductive potential is warranted*	N/A
Step 2. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* Data from {type of study}, including approximately {number} pregnancies, exposed during {Y trimester}, <show > <suggest > an approximately {number}-fold increase in {main adverse pregnancy outcome(s)} corresponding to {concrete data/numbers; excess risk estimates (if possible); pattern of {main adverse pregnancy outcome(s)} observed; existence of dose-related effects}, compared with {reference/comparator group, confidence intervals and background frequency, as applicable}.	*[Pregnancy]* <In <very> rare cases>, this medicine may increase the risk of <birth defects <such as {list the side effects}>>< {main adverse pregnancy outcome(s)}> when taken during pregnancy.
Option 2	*[Section 4.6]* Based on <human experience {describe type of experience shortly}> <and> <or> <mechanism of action>, {active substance} <increases> <may increase> the risk of embryo-fetal harm when administered during pregnancy.	
Option 3	*[Section 4.6]* There are no or limited data from the use of {active substance} in pregnant individuals.	N/A
Non-clinical data **Option 1**	*[Section 4.6]* Non-clinical data have sown developmental toxicity, including <malformations><embryo-fetal lethality><peri/postnatal mortality> (see section 5.3).	N/A
Option 2	*[Section 4.6*] Based on non-clinical data <from developmental toxicity studies and/or mechanism of action> (see section 5.3) {active substance} <increases> <may increase> the risk for embryo-fetal harm when administered during pregnancy.	
Option 3	*[Section 4.6]* Non-clinical data are insufficient with respect to developmental toxicity (see section 5.3).	

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
Option 4	*[Section 4.6]* Non-clinical data do not indicate developmental toxicity (see section 5.3).	
Step 3. Select further risk minimisation measures (<> bracket indicates to select as appropriate to the product, risk and indication)		
<Pregnancy testing>	*[Section 4.6 <section 4.4>]* <In females of reproductive potential, a pregnancy test should be considered before starting treatment.>	*[Pregnancy]* <If you can become pregnant, you should considering take a pregnancy test before starting treatment with this medicine.>
<Counselling>	*[Section 4.6 <section 4.4>]* Females of reproductive potential must be advised about the risks of using {active substance} during pregnancy and about the risk minimisation measures to avoid use during pregnancy <including contraceptive measures>.	*[Pregnancy]* Your doctor should tell you about risks of <taking><using> this medicine during pregnancy and should advice you about use during pregnancy, if you can become pregnant.
<When pregnancy is considered during treatment>	*[Section 4.6 <section 4.4>]* If an individual using {active substance} plans to become pregnant, treatment may need to be discontinued <, and, if needed, switched to an alternative treatment> before contraception is discontinued. To facilitate this, -<the individual should be advised to consult the physician as soon as planning pregnancy>. -<a specialist experienced in the management of {the indication for the product} may be consulted>.	*[Pregnancy]* If you are planning to become pregnant during the use of this medicine, treatment with this medicine may need to be stopped <, and, if needed, switched to another medicine> before stopping birth control. < Your doctor will discuss with you your treatment needs and suitable treatment alternatives.> Do not stop <taking><using> your birth control method before you have discussed it with your doctor. *[Pregnancy]* <Talk to your doctor <or to a specialist experienced in {the indication for the product}> as soon as you plan to become pregnant.> *[Pregnancy]* <Discuss <with your doctor> whether <taking><using> this medicine during pregnancy is suitable for you, considering your treatment needs and any potential side effects to the child. The doctor may suggest switching to another medicine.>
<Unplanned pregnancy during treatment>	*[Section 4.6 <section 4.4>]* If an individual becomes pregnant while using {active substance}: -<the individual should be advised to urgently consult the physician>. -<the individual should be advised to immediately cease treatment with {active substance}.>	*[Pregnancy]* If you discover that you are pregnant while taking this medicine, - <talk to your doctor immediately for advice. Do not delay seeking medical guidance.> - <do not stop <taking><using> this medicine on you own, as your condition may become worse. > - <your doctor may tell you to stop treatment immediately>

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	-<the individual must be immediately referred to a specialist to re-evaluate treatment with {active substance} and consider alternative options>. The individual should be referred for evaluation and counselling regarding the exposed pregnancy.	-<your doctor will urgently refer you to a specialist experienced in treating {the indication for the product}. The specialist will reassess your treatment and consider another medicine for you. *[Pregnancy]* < Discuss <with your doctor> whether <taking><using> this medicine during pregnancy is suitable for you, considering your treatment needs and any potential side effects to the child. The doctor may suggest switching to another medicine.>
<u>Recommendation 3:</u> Use of the medicinal product during pregnancy may be considered		
	[Section 4.6] The use of {active substance} may be considered <during pregnancy><during the {number} trimester of pregnancy>.	*[Pregnancy]* Discuss with your doctor whether this medicine is right for you during pregnancy, considering your treatment needs and any potential side effects to the child
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* Data from {type of study}, including approximately {number} pregnancies, exposed during {number} trimester, do not suggest an increased risk of adverse pregnancy outcomes; however, available data are insufficient to draw firm conclusions.	*[Pregnancy]* The effects of this medicine on a child are yet not clear, but current knowledge suggests that there is no risk to the child. *[Pregnancy]* Use of this medicine may therefore be considered <during pregnancy><during the <first><last> <3 months><6 months> of pregnancy><up to {number} weeks <after><before> treatment>.
Option 2	*[Section 4.6]* There are no or limited data from the use of {active substance} in pregnant individuals.	N/A
Non-clinical data **Option 1**	*[Section 4.6]* Non-clinical data are insufficient with respect to developmental toxicity (see section 5.3).	N/A
Option 2	*[Section 4.6]* Non-clinical data have shown developmental toxicity not considered clinically relevant (see section 5.3).	
Option 3	*[Section 4.6]* Non-clinical data do not indicate developmental toxicity (see section 5.3).	
<u>Recommendation 4:</u> Medicinal product can be used during pregnancy		

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	[Section 4.6] {Active substance} can be used <during pregnancy><during {trimester} of pregnancy >	*[Pregnancy]* You can use this medicine during <pregnancy> <the <first><last><3 months><6 months> of pregnancy>.
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* Data from {type of study}, including approximately {number} pregnancies, exposed during {number trimester}, do not indicate an increased risk of {main adverse pregnancy outcome(s)}, based on {brief summary of findings}.	N/A
Option 2	*[Section 4.6]* A large amount of data from pregnant individuals {approximate number} indicates no increased risk of adverse embryo-fetal or neonatal effects.	
Option 3	*[Section 4.6]* No effects are anticipated during pregnancy since systemic exposure to {active substance} is negligible.	

Table 2. Breastfeeding

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	<u>Recommendation 1:</u> The medicinal product is contraindicated during breastfeeding	
	[Section 4.3] Breastfeeding (see section 4.6). *[Section 4.6]* {Active substance} is contraindicated during breastfeeding (see section 4.3). Breastfeeding must be discontinued during treatment with {active substance}.	*[Do not <take> <use> X]* If you are breastfeeding. *[Breastfeeding]* Do not breastfeed during treatment with this medicine. You must stop breastfeeding before treatment with this medicine.
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* <{Active substance} <metabolites> have been detected in human breast milk in high amount. Serious adverse reactions <such as {give examples of reported adverse reactions}> have been reported in breastfed infants of treated mothers.> <Although {Active substance} <metabolites> have been detected in human breast milk in low amount, serious adverse	*[Breastfeeding]* <This medicine passes into breast milk in high amounts that reach the breastfed child. Serious side effects <such as {give examples of reported side effects}> have been reported in breastfed children whose mothers used <invented name>.> <Although this medicine passes into breast milk in low amounts, serious side effects <such as {give examples of reported side

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
	reactions <such as {give examples of reported adverse reactions}> have been reported in breastfed infants of treated mothers.> <{Active substance} <metabolites> are excreted into human milk to such an extent that serious adverse reactions in the breastfed infant are likely.>	effects}> have been reported in breastfed children whose mothers used <invented name>.> *[Breastfeeding]* <This medicine passes into breast milk and is likely to cause serious side effects <such as {give examples of reported side effects}> in a breastfed child.>
Option 2	*[Section 4.6]* <Physicochemical data suggest excretion of {active substance} <metabolites> in breast milk><which could lead to clinically relevant systemic exposure of the breastfed infant >.> <Serious adverse reactions in the breastfed infant are likely>.	
<u>Recommendation 2:</u> Medicinal product should not be used during breastfeeding		
	[Section 4.6] {Active substance} should not be used during breastfeeding.[OR] <Breastfeeding should be discontinued during treatment with {active substance}>	*[Breastfeeding]* <This medicine should not be used during breastfeeding.> <You should stop breastfeeding before treatment with this medicine.> *[Breastfeeding]* Do not breastfeed during treatment with this medicine. You must stop breastfeeding before treatment with this medicine.
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* <{Active substance} <metabolites> have been detected in human breast milk in <minimal> <low> <high> amount. Adverse reactions <such as {give examples of reported adverse reactions}> have been reported in breastfed infants of treated mothers.> <{Active substance} <metabolites> are excreted into human milk to such an extent that adverse reactions on the breastfed infant are possible.>	*[Breastfeeding]* <This medicine passes into breast milk <minimal><low><high> amounts and reaches the breastfed child. Side effects <such give examples of reported side effects}> have been reported in breastfed children whose mothers used this medicine.> <This medicine passes into breast milk and is possible to cause side effects <such as {give examples of reported side effects}> in the breastfed child.>
Option 2	*[Section 4.6]* <Physicochemical data suggest excretion of {active substance} <metabolites> in breast milk><which could lead to clinically relevant systemic exposure of the breastfed infant.> <Adverse reactions in the breastfed infant are possible.>	
Non-clinical data	*[Section 4.6]* It is unknown whether {active substance} <metabolites> are excreted in human milk. Non-clinical data have shown toxicity <from developmental toxicity studies	N/A

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
Option 1	and/or mechanism of action><such as {concrete adverse effects}> (see section 5.3).	
<u>Recommendation 3:</u> Use of the medicinal product during breastfeeding may be considered		
	[Section 4.6] The use of {active substance} may be considered during breastfeeding. A decision whether to breastfeed while using {active substance} should take into account both the benefit of breastfeeding and the potential risk of adverse reactions in the infant.	*[Breastfeeding]* Discuss with your doctor whether this medicine is right for you while breastfeeding, considering the benefits of breastfeeding and any potential side effects for your child.
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* <It is unknown whether {active substance} <metabolites> are excreted in human milk.> Alternatively: < {active substance} <metabolites> are excreted in human milk in low levels.> <Serious adverse reactions on a breastfed infant are not expected>	*[Breastfeeding]* <It is unknown if this medicine passes into the breast milk.> Alternatively: <This medicine passes into the breast milk in low amounts.> <Serious side effects in the breastfed child are not expected.>
Option 2	*[Section 4.6]* <{Active substance} is not expected to be absorbed from infant´s gastrointestinal tract.>	*[Breastfeeding]* < This medicine passes into breast milk, however, it is not expected to pass from your child's stomach and intestines into their blood stream.>
Option 3	*[Section 4.6]* <Physicochemical data suggest excretion of {active substance} <metabolites> in breast milk><which could lead to clinically relevant systemic exposure of the breastfed infant> <Serious adverse reactions on a breastfed infant are not expected>.	*[Breastfeeding]* <This medicine may pass into the breast milk.> <Serious side effects in the breastfed child are not expected.> Breastfeeding may be considered while you are <taking><using> this medicine.
<u>Recommendation 4:</u> Medicinal product can be used during breastfeeding		
	[Section 4.6] {Active substance} can be used during breastfeeding.	*[Breastfeeding]* You can use this medicine while breastfeeding.
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* <No effects of {active substance} have been shown in breastfed infants of treated mothers.>	*[Breastfeeding]* <No side effects have been shown in breastfed children whose mothers <used><received> this medicine.>

Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
Option 2	*[Section 4.6]* <No effects on the breastfed infant are anticipated since the systemic exposure of {active substance} on the breastfed infant is negligible.>	*[Breastfeeding]* <Side effects in the breastfed child are not anticipated.>
Option 3	*[Section 4.6]* <{Active substance} <metabolites> are excreted in human milk, but at therapeutic doses of {active substance} no effects on the breastfed infant are anticipated.> <Serious adverse reactions on the breastfed infant are unlikely.>	*[Breastfeeding]* <Serious side effects in the breastfed child are unlikely.>
Breastfeeding recommendations for specific medicinal products		
Monoclonal antibodies	*[Section 4.6]* <It is unknown whether {active substance} is excreted in human breast milk. Human IgGs are known to be excreted in breast milk for a few days after birth, declining to low levels thereafter. Therefore, exposure of the breastfed infant <and a risk for adverse reactions> is possible during the initial days after birth.> *[Considering the major elements of assessment, the following sentence may also be included]* *[Breastfeeding]* <Beyond this period, use of {active substance} during breastfeeding may be considered.>	*[Breastfeeding]* <It is not known whether this medicine passes into breast milk. Some natural antibodies (a type of protein) pass into breast milk for a few days after birth, but their levels drop quickly after this time. Because of this, a possible risk to a breastfeeding newborn during those first few days after birth cannot be fully ruled out. > [breastfeeding] <After the first few days, breastfeeding may be considered> *[Breastfeeding]* <Talk to your doctor about whether to use this medicine while breastfeeding, considering the benefits of breastfeeding, your treatment needs, and the potential risks of side effects to your child.>
Protein-based therapeutics	*[Section 4.6]* <It is unknown whether {active substance} is excreted in human breast milk. However, protein-based products are expected to be denatured and degraded in the infant's gastrointestinal tract.> *[Considering the major elements of assessment, the following sentence may also be included]* *[Breastfeeding]* < Use of {active substance} during breastfeeding may be considered.>	*[Breastfeeding]* <It is not known whether this medicine passes into breast milk. However, medicines made from proteins are expected to be broken down in the child's body and are unlikely to affect the child. Because of this, breastfeeding can be considered while you are <taking><using> this medicine.> <Talk to r your doctor to discuss if you should use this medicine while breastfeeding, considering the benefits of breastfeeding, your treatment needs, and the potential risks of side effects to your child.>

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Steps drafting sentences	Template sentences for SmPC	Template sentences for PL section 2
Step 1. Select most suitable text describing available data		
Clinical data **Option 1**	*[Section 4.6]* <Based on the mechanism of action of {active substance}, there is a risk for impaired fertility in <both><males> <and> <or> <females>.>	There is a risk that this medicine <temporarily><permanently> affects your ability to <get pregnant><father a child>. <Discuss with your doctor before you <take><use> this medicine if you are planning to have a child.>
Option 2	*[Section 4.6]* <Clinical data <show> <suggest> risk of <reversible><irreversible> <impaired fertility> after treatment with {active substance} in <both><males> <and> <or> <females>.	
Option 3	*[Section 4.6]* <There is no human data with respect to fertility.>	No statement needed
Non-clinical data **Option 1**	*[Section 4.6]* <Non-clinical data with {active substance} have shown <reversible> <irreversible> adverse effects on fertility in <both><males> <and> <or> <females> (see section 5.3).>	There is a risk that this medicine <temporarily><permanently> affects your ability to <get pregnant><father a child>. <Discuss with your doctor before you <take><use> this medicine if you are planning to have a child.>
Option 2	*[Section 4.6]* <Findings from non-clinical data indicate that {active substance} may impair <both><males> <and> <or> <females> fertility (see section 5.3).>	N/A
Option 3	*[Section 4.6]* <Fertility studies with {active substance} were not performed in animals.>	
Option 4	*[Section 4.6]* < Findings from non-clinical data with {active substance} are inconclusive on <both><males> <and> <or> <females> fertility (see section 5.3).>	
Option 5	*[Section 4.6]* <Non-clinical data with {active substance} <have not shown><do not suggest> any adverse effects on fertility in <both><males> <and> <or> <females>> (see section 5.3).	

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