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Guideline on good pharmacovigilance practices (GVP)

Module XVI Addendum I~~II~~ – ~~Pregnancy prevention programme and other pregnancy-specific~~ R~~r~~isk minimisation measures for medicinal products with embryo-fetal risks

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* This revised final guidance is applicable to new applications for marketing authorisation, new risk minimisation measures and new studies evaluating risk minimisation measures for authorised medicinal products but not immediately applicable to existing risk minimisation measures and ongoing activities regarding risk minimisation measures; however, where existing risk minimisation measures are amended, the revised guidance should be taken into account.

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

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

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

Note: This Addendum to GVP Module XVI has been renumbered from Addendum III (the number it carried as the draft version for public consultation) to Addendum I (the number of the final version), following revision 3 of GVP Module XVI finalised in 2024 (in which the previous Addendum I on educational materials was integrated as envisaged at the time of issuing the previous Addendum I).

In response to the public consultation, the final version includes the following:

- Alignment of structure and terminology with revision 3 of Module GVP XVI;

- Addition of an explicit statement on the overall guiding principle that risk minimisation measures for embryo-fetal risks should not compromise addressing the medical needs of a patient when there is no suitable alternative treatment available;

- Deletion of overlap with the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling and clarification of the interface between these two guidance documents;

- Clarifications on the actions to avoid becoming pregnant for risk minimisation, where needed, when using a medicinal product with embryo-fetal risks;

- Introduction of core elements to define pregnancy prevention programmes (PPP) for tailoring PPPs, where needed, to the clinical situation typical for the given medicinal product;

- Overall editing for clarity.

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XVI.Add.I~~I~~II.1. Introduction

~~A pregnancy prevention programme (PPP) is a set of routine and additional risk minimisation measures (RMM) that aims at minimising exposure to a medicinal product during pregnancy (see GVP Module XVI). More specifically, the aim of a PPP is to prevent the exposure of the unborn child by ensuring that female (adolescent and adult) patients are not pregnant at the start of treatment and to ensure that they do not become pregnant during the course of treatment, or also during a defined period after the treatment has been discontinued. A PPP is to be considered in situations where the product has the potential for a teratogenic effect or an adverse effect on the (neuro)development of the child through exposure in utero (where in this document reference is made to teratogenicity, it is meant, for the ease of reading, to include (neuro)developmental effects). A full description of the elements of the PPP is provided in XVI.Add.III.3.~~

~~Although rarely required, a PPP could also include targeting male patients when there is evidence that use of a medicinal product by the biological father can have a teratogenic effect via semen during conception.~~

~~As described in XVI.Add.III.2., selected pregnancy-specific routine RMM (see CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[1]) and, possibly, additional RMM may be required instead of a PPP.~~

This Addendum to GVP Module XVI provides guidance on risk minimisation measures (RMM) aiming at:

- Preventing exposure of an embryo/fetus, at conception or in utero, to a medicinal product which has an identified or potential risk of embryo-fetal toxicity; or
- Minimising embryo-fetal risks if such exposure of an embryo/fetus to such a medicinal product may have occurred.

Embryo-fetal toxicity may manifest as adverse reactions in the embryo/fetus/neonate/infant/child, including a congenital anomaly, e.g. a birth defect or an adverse effect on the development, such as the neuro- or endocrine development, a miscarriage or a death of the embryo/fetus/neonate (see GVP Annex I).

The overall guiding principle is that RMM for embryo-fetal risks should not compromise addressing the medical needs of a patient[2] when there is no suitable alternative treatment available. Patients and healthcare professionals should be adequately informed about the risks and the intended actions for minimising the risks.

The patient target populations of the RMM may be:

- Females (or individuals) who have reproductive potential;

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

[2] Here, the term 'patient' refers to the individual using or considering the use of a medicinal product for their medical condition. Notwithstanding, in general, an embryo/foetus/born child who may have been adversely affected by a medicinal product at conception or in utero through maternal use of the product is also considered a patient (see GVP Annex I).

- Females (or individuals) who have or suspect to have become pregnant while using the medicinal product;
- Males (or individuals) where seminal fluid may carry potentially harmful levels of the active substance contained in the medicinal product or where the semen/germ cell may be harmed by the product;
- Children/adolescents with a view to their future reproductive potential;
- Individuals who use the medicinal product and intend to donate blood, to deter their blood donation to avoid a pregnant female receiving such blood donation;
- Parents of minor patients/carers of patients described above, as applicable.

This guidance mainly focusses on the female patient target populations, because embryo-fetal risks via the male patient are rare (as far as evidenced to date). However, for this latter case, the guidance can be used as applicable.

The healthcare professional target populations of the RMM include physicians, midwives, nurses and pharmacists, depending on the intended actions for risk minimisation and the role of the different healthcare professionals in the healthcare systems of Member States (e.g. in some Member States prescribing allowance for midwives is in place or pharmacists can be required to perform specific tasks during dispensing). For the RMM to be implemented effectively in healthcare with a patient-centred approach, collaboration across healthcare will be necessary (e.g. treatment of the medical condition, risk counselling and prescribing of contraceptive measures may be conducted by different healthcare professionals).

This guidance describes the options of intended actions for risk minimisation in XVI.Add.I.2. and the tools of risk minimisation in XVI.Add.I.3.. The actions and tools should be combined as considered needed for the concerned medicinal product. In exceptional situations, actions and tools may be required to form a pregnancy prevention programme (PPP) (see XVI.Add.I.3.2.3.).

This guidance is an Addendum to GVP Module XVI and should be read together with this as well as other GVP Modules and guidelines as referenced, in particular the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[3]. This latter guideline provides guidance on risk assessment, criteria for a contraindication taking into account medical needs and wording for the product information.

~~XVI.Add.III.2. Criteria for requiring a PPP or selecting pregnancy-specific risk minimisation measures~~

~~The decisive criteria for requiring a PPP (or selected pregnancy-specific RMM instead) should always be:~~

- ~~Level of scientific evidence for the teratogenic potential of a medicinal product in humans, including the evidence on the magnitude and nature of the teratogenic effect; and~~

[3] www.ema.europa.eu

- Context of the likely use of the medicinal product (see also CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[4]).

Both these criteria should be re-assessed regularly.

The need for a PPP (or selected pregnancy-specific RMM instead) should be risk-proportionate in relation to the magnitude and nature of the teratogenicity (e.g. frequency, type or outcome of malformation) and may change when new evidence emerges.

The Agency and competent authorities in Member States can propose further measures on a case-by-case basis and as applicable.

Depending on the assessment of the two criteria, the following most typical scenarios and requirements are foreseen:

A) Proven or strongly suspected teratogenicity

If a medicinal product is proven or strongly suspected to be teratogenic in humans and is expected to be used in women of childbearing potential under the clinical conditions for which the product is authorised, and the magnitude and nature of the teratogenicity are significant, a PPP is considered necessary (see XVI.Add.III.3.).

Where the magnitude and nature of the teratogenicity do not justify a PPP (but the first two criteria are fulfilled), additional pregnancy-specific RMM are considered necessary, in addition to advice in the summary of product characteristics (SmPC) and package leaflet (PL) as routine RMM (see CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[5]). As a minimum, these additional pregnancy-specific RMM should include, usually supported by educational materials for both patients and healthcare professionals, the following:

- Personal patient counselling by a healthcare professional;
- Pregnancy testing before the start of treatment and, as applicable, also during and after treatment; and
- Application of effective contraceptive measures.

If the use of the product by women of childbearing potential under the clinical conditions for which the product is authorised is considered unlikely (but the criterion of proven or strongly suspected teratogenicity in humans is fulfilled), routine RMM alone are usually considered appropriate.

If the likelihood of the use of the product in women of childbearing potential is difficult to predict, additional pregnancy-specific RMM may still be required, based on the assessment.

[4] www.ema.europa.eu
[5] www.ema.europa.eu

B) Possible but unconfirmed teratogenicity

If the available evidence suggests possible teratogenicity of a medicinal product, but a causal relationship between harm in children and the in-utero exposure to the product has not been confirmed or is not strongly suspected, the decision on whether to require additional pregnancy-specific RMM in addition to advice in the product information as routine RMM (see CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[6]) should take into account the following considerations:

- Teratogenicity of the product is known or suspected from animals, but there is insufficient, inconclusive or no evidence in humans;
- Type or outcome of malformation in animals; and
- Use in women of childbearing potential is expected under the clinical conditions for which the product is authorised.

In principle, in most cases of possible but unconfirmed teratogenicity, it is expected that routine RMM will be sufficient.

Additional pregnancy-specific RMM may still be required, based on the assessment.

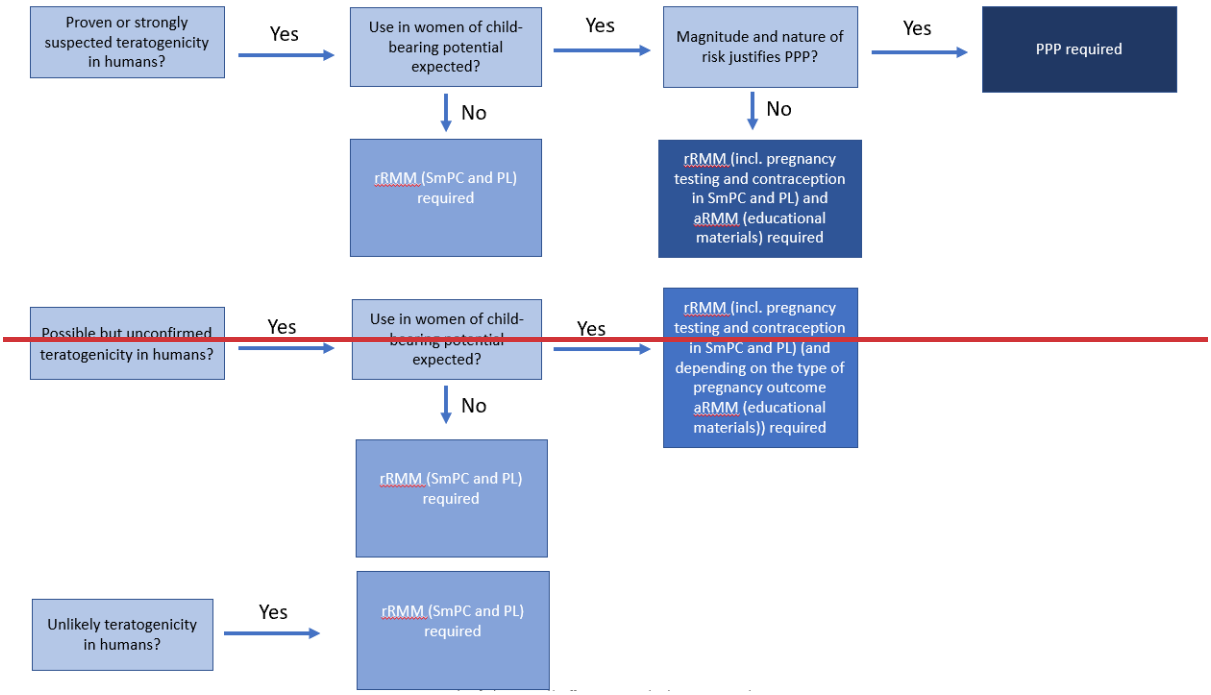
C) Unlikely teratogenicity

If teratogenicity of a medicinal product in humans is considered unlikely and if the use of a medicinal product in women of childbearing potential is considered unlikely under the clinical conditions for which the product is authorised (e.g. a product for treating prostate cancer), additional pregnancy-specific RMM are not considered appropriate.

However, routine RMM are still considered appropriate, in particular if the use of the medicinal product in women of childbearing potential may occur, even if very rarely, or is difficult to predict.

Schematically, the considerations determining whether a PPP or selected pregnancy-specific RMM are necessary are depicted for the most typical scenarios in Figure XVI.Add.III.1..

[6] www.ema.europa.eu



~~Figure XVI.Add.III.1: Overview of considerations for requiring a PPP or selected pregnancy-specific RMM in the most typical scenarios~~

~~XVI.Add.III.3. Risk minimisation measures constituting a PPP~~

~~A pregnancy prevention programme (PPP) is a set of routine and additional risk minimisation measures (RMM). In principle, a PPP should include all the following pregnancy-specific RMM, which need to fulfil the requirements described in GVP Module XVI:~~

- ~~Summary of product characteristics (SmPC) and package leaflet (PL) with the following:~~
  - ~~Contraindication in pregnancy;~~
  - ~~Contraindication in women of childbearing potential who are not applying effective contraceptive measures; and~~
  - ~~Information on the teratogenic risks of the product and related recommendations in the sections on warnings (i.e. SmPC section 4.4 and PL section 2) and on pregnancy (i.e. SmPC section 4.6 and PL section 2), which may also include criteria defining women who are not of childbearing potential[7] (see CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling[8]);~~

[7] ~~Women generally considered not to be of child-bearing potential include those:~~
- ~~aged 50 years or above and being naturally amenorrhoeic for at least 1 year (note: amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential);~~
- ~~with premature ovarian failure confirmed by a specialist gynaecologist;~~
- ~~having undergone bilateral salpingo-oophorectomy or hysterectomy; or~~
- ~~being affected by XY genotype, Turner syndrome or uterine agenesis.~~

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

- Required conditions of prescribing (as also defined in the SmPC and PL and referred to in educational materials) including the following:
  - Before treatment start:
    - Assessment of the patient's potential for becoming pregnant and for following the PPP; and
    - Personal counselling session of the patient by a healthcare professional on:
      - teratogenic risks of the product;
      - need to avoid pregnancy while using the product and to apply effective contraceptive measures;
      - importance of discussing with a healthcare professional if the wish for conceiving a child exists; and
      - time after treatment discontinuation during which pregnancy will also need to be avoided (where the active substance and/or its metabolites (if teratogenic) have a long half-life; usually this would be five times the half-life of the active substance)
  - At treatment start:
    - Confirmation of absence of pregnancy through a recent negative pregnancy test, unless one criterion for considering that the woman is not of childbearing potential is met (see Footnote 6); and
    - Counselling on effective contraceptive measures
  - During treatment:
    - Confirmation of absence of pregnancy at an appropriate frequency, normally through a negative pregnancy test, unless one criterion for considering that the woman is not of childbearing potential (see Footnote 6) is met; and
    - Reminder personal counselling sessions on:
      - need to avoid pregnancy while using the product and to apply effective contraceptive measures;
      - importance of discussing with a healthcare professional if the wish for conceiving a child emerges; and
      - the reasons why counselling sessions are needed with the frequency considered appropriate given the context of product use
  - At treatment end, taking into account the half-life of the active substance and its teratogenic metabolites:
    - Confirmation of absence of pregnancy at an appropriate frequency, normally through a negative pregnancy test, unless one criterion for considering that the woman is not of childbearing potential (see Footnote 6) is met; and
    - Reminder personal counselling session on:
      - time period during which pregnancy will also need to be avoided
- Required conditions of dispensing (as also defined in the SmPC and PL and referred to in educational materials), e.g.:

- Dispensing within a limited number of days after the prescription date;
- Dispensing a limited quantity of product to ensure that treatment start is aligned with a negative pregnancy test (how this is achieved can differ between Member States);
- Accessibility to the dispenser of the confirmation that the patient has been counselled regarding the teratogenic risks and understands the need to avoid product use during pregnancy in line with the recommendations from competent authorities in Member States;
- No allowance for free samples of the product;

- Educational materials targeting healthcare professionals (e.g. in guides, checklists or other materials as applicable, see GVP Module XVI) which includes key information on the following:
  - Teratogenic risks of the product;
  - Required pregnancy testing, the required conditions of prescribing and dispensing and the required personal counselling of the patient;
  - Need to ensure that effective contraceptive measures are applied; and
  - Guidance on how to act in the case of pregnancy and how to help ensure that any possible pregnancy outcomes are evaluated appropriately;

- Educational materials targeting patients which includes key information on the following:
  - Teratogenic risks of the product;
  - Required actions to avoid use of the product during pregnancy, e.g. applying effective contraceptive measures;
  - Need for a negative pregnancy test result to be verified by a healthcare professional before treatment start and be repeated at suitable intervals during and after treatment if applicable;
  - Guidance on the need to consult a healthcare professional in the case of pregnancy;
  - Counselling before treatment start and regularly during and after treatment, and also in the event of a pregnancy (with evaluation of the outcome of any pregnancy); and
  - Handling of any unused product in line with Member States and local procedures to avoid misuse and accidental exposure (including advice to return unused medicine at the end of treatment to the physician or pharmacist)

The abovementioned items can be conveyed by the use of RMM tools such as guides, patient cards or risk awareness forms (see GVP Module XVI), in particular:

- Patient card with key messages acting as a reminder of:
  - teratogenic risks of the product;
  - need to avoid use of the product during pregnancy; and
  - associated PPP requirements

Where there are other important identified risks with the product to be displayed on a patient card, the information on teratogenicity must be clearly visible; only in very exceptional circumstances may it be necessary to have a separate patient card on teratogenicity.

- Risk awareness form for each patient to confirm the patient has been fully informed of the teratogenic risk of the product and understands the need to avoid product use during pregnancy.

The format of such a risk awareness form, e.g. electronic in addition to paper-based materials or recording in the patient's medical record, will depend on what is most suitable given the context of product use and the applicable legal framework of each Member State.Further, when requiring a PPP, the following pregnancy-specific RMM should be considered to become part of the PPP:

- Labelling of the outer packaging that includes an explicit statement in words on the need to avoid pregnancy when using the product (e.g. "CAN SERIOUSLY HARM AN UNBORN BABY. Women must use effective contraception. Do not use if you are pregnant or think you may be pregnant.") via a visual reminder such as a boxed warning or a pictogram (the details of the visual reminder should be agreed at Member States' level and be subject to a user test taking into account input from local patient representatives);
- As needed, a direct healthcare professional communication (DHPC) (see GVP Module XV) about the PPP can become part of a PPP if a new active substance, new population, or a newly identified teratogenic risk is concerned.

On a case-by-case basis, considering relevant aspects of the risk/safety profile and the treatment setting of the medicinal product, a controlled access programme in line with GVP Module XVI, may be required in addition to a PPP.

Because of differences between healthcare systems in Member States, some of the routine and additional RMM listed above may need to be implemented in different ways in Member States.

XVI.Add.I.2. Intended actions for risk minimisation applied to embryo-fetal risks

Following assessment of a medicinal product in accordance with the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[9], its product information may be required to contain a:

- Contraindication, recommendation or precautionary advice not to use the product during pregnancy (the whole period of pregnancy or the relevant period of gestation); and/or a
- Recommendation or precautionary advice to use the product in female patients who have reproductive potential only when actions to avoid becoming pregnant (see XVI.Add.I.2.1.2.) are taken.

For the concerned medicinal products, intended actions to prevent exposure of an embryo/fetus, at conception or in utero, to a concerned product (see XVI.Add.I.2.1.) and intended actions in the case such exposure may have occurred (see XVI.Add.I.2.2.) may be required.

[9] www.ema.europa.eu

XVI.Add.I.2.1. Intended actions to prevent exposure of an embryo/fetus to a medicinal product with embryo-fetal risks

The actions intended to be taken by patients or healthcare professionals for risk minimisation to prevent exposure of an embryo/fetus at conception or in utero to a medicinal product with embryo-fetal risks include, but may not be limited to, the following options:

XVI.Add.I.2.1.1. Risk counselling

Risk counselling of the female patient (involving their parents/carers as applicable) is to be conducted by a healthcare professional in a personal dialogue and aiming at ensuring the patient's full understanding.

It is essential that this action is integrated in the therapeutic decision-making at the time of first prescription. This action may also be required during and after use of the medicinal product as a reminder and support, taking into account the patient's (changing) reproductive potential, engagement in activities that could lead to becoming pregnant and/or consideration of a pregnancy.

Risk counselling includes information on and the opportunity for questions from the patient about the:

- Embryo-fetal risks of the medicinal product;
- Need to manage the patient's medical condition, the treatment options and the risks of the medical condition for a potential embryo/fetus;
- Actions to avoid becoming pregnant during and after use of the medicinal product, including options of contraceptive measures (see XVI.Add.I.2.1.2.) and other intended actions for risk minimisation, e.g. those described in XVI.Add.I.2.;
- Need to promptly contact the prescribing healthcare professional if questions regarding the treatment, the embryo-fetal risks of the medicinal product or the RMM arise;
- Need for consultation by an experienced or specialist physician if the patient is considering a pregnancy or if exposure of an embryo/fetus to the concerned medicinal product may have occurred, to discuss the embryo-fetal risks and actions for managing the patient's medical condition and minimising the embryo-fetal risks (see XVI.Add.I.2.2.).

Risk counselling may be based on educational/safety advice material(s) (see XVI.Add.I.3.2.) and includes providing the patient with these materials, where these are required for the medicinal product.

XVI.Add.I.2.1.2. Taking actions to avoid becoming pregnant

Actions to avoid becoming pregnant to be taken by a female patient who has reproductive potential when using the medicinal product are to not engage in activities that could lead to

becoming pregnant or to apply contraceptive measures. Furthermore, the patient should contact the prescribing healthcare professional before stopping the actions to avoid becoming pregnant.

Actions to avoid becoming pregnant are to be taken during the use of the medicinal product and after its use for as long as it is estimated that exposure of an embryo/fetus could occur, taking into account the pharmacokinetic properties of the product (if applicable, see SWP/NcWP Recommendations on the Duration of Contraception Following the End of Treatment with a Genotoxic Drug[10]).

Actions for risk minimisation intended to be taken by healthcare professionals, to support the patient in this respect, may include:

- Assessment of the reproductive potential and risk counselling (see XVI.Add.I.2.1.1.);
- Prescription of effective contraceptive measures as applicable; and
- Providing the patient with educational/safety advice material(s) (see XVI.Add.I.3.2.).

If a medicinal product may reduce the effectiveness of hormonal contraceptives, this interaction should be mentioned in section 4.5 of the SmPC and section 2 of the package leaflet (see Guideline on Summary of Product Characteristics[11] and the Template for the Package Leaflet[12]).

XVI.Add.I.2.1.3. Pregnancy testing

Pregnancy testing is to ensure excluding pregnancy before initiating the medicinal product and, as needed, also during treatment, e.g. at time of re-prescribing, and, as needed, after treatment, taking into account the pharmacokinetic properties of the product.

XVI.Add.I.2.1.4. Supervising treatment by an experienced or specialist physician

Supervising treatment by an experienced or specialist physician is to ensure that the use of the medicinal product is initiated and overseen by a physician who is experienced in the management of the medical condition and the use of the concerned medicinal product and can give due consideration to possibly suitable alternative treatment(s).

XVI.Add.I.2.1.4.1. Conducting regular medication reviews

Supervising treatment may include regular medication reviews, e.g. at an annual basis depending on the duration of treatment, to examine changes in the medical condition and the need for the medicinal product and to consider possibly suitable alternative treatment(s), in particular if reproductive potential or the consideration of a pregnancy emerges.

[10] www.ema.europa.eu
[11] European Commission; https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en#volume-2c---regulatory-guideline
[12] www.ema.europa.eu

XVI.Add.I.2.1.5. Avoiding blood and semen/sperm donation

Occasionally, it may be appropriate to deter patients from donating blood during and for a specified period after use of the medicinal product, to avoid in utero exposure of the embryo/fetus due to a pregnant female receiving a blood donation.

Likewise, it may be appropriate to deter patients from donating semen/sperm during and for a specified period after use of the medicinal product.

XVI.Add.I.2.2. Intended actions if exposure of an embryo/fetus to a medicinal product with embryo-fetal risks may have occurred

If exposure of an embryo/fetus, at conception or in utero, to a medicinal product with embryo-fetal risks has or is suspected to have occurred, the patient should be advised to contact the prescribing healthcare professional promptly (see XVI.Add.I.2.1.1.).

Appropriate actions for an experienced or specialist physician to take for managing the patient's medical condition and minimising embryo-fetal risks after discussion with the patient may include, but may not be limited to, the following options:

- Interrupting the use of the medicinal product;
- Switching to suitable alternative treatment;
- Dose reduction;
- Specific prenatal monitoring.

XVI.Add.I.3. Tools of risk minimisation measures applied to embryo-fetal risks

XVI.Add.I.3.1. Tools of routine risk minimisation measures

For a medicinal product with embryo-fetal risks, these risks and the actions intended for risk minimisation (see XVI.Add.I.2.) are described in the summary of the product characteristics (SmPC) and the package leaflet in accordance with the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling[13], the Guideline on Summary of Product Characteristics[14] and the Template for the Package Leaflet[15]. The SmPC is the fundamental routine RMM tool, and its information is the basis for other routine and, where required, additional RMM (see XVI.Add.I.3.2.). Further routine RMM tools include the labelling of immediate and outer packaging, the pack size and the classification of the medicinal product (legal status).

[13] www.ema.europa.eu
[14] European Commission; https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en#volume-2c---regulatory-guideline
[15] www.ema.europa.eu

In addition to the guidance on routine RMM tools and materials in GVP Module XVI, the following applies:

XVI.Add.I.3.1.1. Visual enhancements, special warnings and information on precautions in the labelling of immediate and outer packaging

The labelling of the outer packaging may include a reminder statement on the need to avoid the use of the medicinal product in pregnancy (e.g. "CAN SERIOUSLY HARM AN UNBORN BABY. Take measures to avoid becoming pregnant. Do not use if you are pregnant or think you may be pregnant."), which may be visually enhanced. Details of visual enhancements should be agreed at the level of Member States, and their user-testing in local contexts is encouraged or may be required.

XVI.Add.I.3.1.2. Disallowing free samples

For a medicinal product with embryo-fetal risks, Member States may disallow free samples of the product.

XVI.Add.I.3.2. Tools of additional risk minimisation measures

To promote risk awareness and adherence to the actions intended for risk minimisation for medicinal products with embryo-fetal risks (see XVI.Add.I.2.), additional RMM tools should be considered, taking into account the risk assessment and the overall context in accordance with the points to consider for requiring and selecting additional RMM tools or for adapting existing additional RMM in GVP Module XVI.

In addition to the guidance on additional RMM materials in GVP Module XVI, the following applies:

XVI.Add.I.3.2.1. Educational/safety advice materials for healthcare professionals

If an educational/safety advice material includes actions for risk minimisation intended to be taken by different healthcare professionals who need to collaborate for the implementation of the RMM (see XVI.Add.I.1.), the materials may have separate sections for specific healthcare professionals.

XVI.Add.I.3.2.2. Educational/safety advice materials for patients

If an educational/safety advice material for patients is to display embryo-fetal risks in addition to information on the other risks with the medicinal product, the information on the embryo-fetal risks should be highly visible, and therefore (a) separate materials(s) on the embryo-fetal risks may be necessary in exceptional situations.

XVI.Add.I.3.2.3. Pregnancy prevention programme (PPP)

In exceptional situations of embryo-fetal risks of a medicinal product, intended actions for risk minimisation (see XVI.Add.I.2.) and RMM tools (see XVI.Add.I.3.) can be combined to form a pregnancy prevention programme (PPP).

The decision to require a PPP should take into account the points to consider in GVP Module XVI and in particular:

- Characteristics of the embryo-fetal risks;
- Indication of the medicinal product, including the prevalence of disease in females with reproductive potential, the typical duration of treatment with the product and the overall clinical context; and
- Existing awareness of the embryo-fetal risks and the actions intended for minimising these risks in current healthcare practice.

A PPP is constituted by requiring at least the following:

- Contraindication, or a contraindication unless there is no suitable alternative treatment for the patient during pregnancy;
- Risk counselling (see XVI.Add.I.2.1.1.);
- Taking actions to avoid becoming pregnant while using the medicinal product, i.e. to not engage in activities that could lead to becoming pregnant or to apply contraceptive measures (see XVI.Add.I.2.1.2.);
- Pregnancy testing (see XVI.Add.I.2.1.3.);
- Supervising treatment by an experienced or specialist physician (see XVI.Add.I.2.1.4.), including conducting regular medication reviews (see XVI.Add.I.2.1.4.1.);
- Reminder statement regarding the embryo-fetal risks on the outer packaging (see XVI.Add.I.3.1.1.);
- Educational/safety advice material(s) for healthcare professionals (see XVI.Add.I.3.2.1.); and
- Educational/safety advice material(s) for patients (see XVI.Add.I.3.2.2.).

A PPP for a concerned medicinal product may include further actions intended to be taken by patients or healthcare professionals for risk minimisation and/or further additional RMM tools, including one or more risk minimisation control tool(s) (see GVP Module XVI).

Actions intended by the PPP should be included in sections 4.3, 4.4 and 4.6 of the SmPC, and a reference to the related additional RMM material(s) should be included in SmPC section 4.4 (see GVP Module XVI and Guideline on Summary of Product Characteristics[16]). Actions intended by the PPP to be taken by the patient should be included in section 2 of the package leaflet, together with reference to the related additional RMM material(s) targeted at patients (see GVP Module XVI and Template for the Package Leaflet[17]).

[16] European Commission; https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en#volume-2c---regulatory-guideline
[17] www.ema.europa.eu

A direct healthcare professional communication (DHPC), as a safety communication tool (see GVP Module XV), may be required to announce or remind healthcare professionals of a new or adapted PPP (see GVP Module XVI).

XVI.Add.I.4. Evaluating risk minimisation measures applied to embryo-fetal risks

The evaluation of effectiveness of RMM addressing embryo-fetal risks should follow GVP Module XVI and GVP Module XVI Addendum II. These include pregnancy-specific guidance on spontaneous reporting of pregnancy-related cases, registries and cohort study designs, including their data sources and calculations of pregnancy incidence during use of a medicinal product. While spontaneous reporting rates of pregnancy-related cases (see GVP Module VI) may be applied to monitor the use of the product in pregnancy, (a) post-authorisation safety study(ies) (PASS) is (are) the preferred approach if feasible, to evaluate the effectiveness of RMM addressing embryo-fetal risks. Such PASS may be a drug utilisation study (DUS), a survey or a mixed methods study.

A DUS can investigate the prescribing patterns of the product in females of typical reproductive age. In the case that the RMM has/have been implemented at the time of marketing launch of the product, a DUS may help to monitor the adherence to RMM over time, e.g. by comparisons of yearly adherence rates to individual action elements of the RMM. If the RMM has/have been introduced during the post-authorisation phase, a DUS may have a pre-/post-intervention evaluation design to compare adherence by healthcare professionals and patients to the intended actions for risk minimisation before and after RMM implementation.

A survey may investigate the dissemination and usefulness of RMM materials as perceived by the RMM target population as well as the adoption of knowledge and adherence to the intended actions for risk minimisation.

A mixed method study may be useful to identify potential barriers and enablers of RMM implementation in clinical practice.