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Guideline on good pharmacovigilance practices (GVP)

Module XVI Addendum I – Risk 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.

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 this 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).

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XVI.Add.I.1. Introduction

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[1] 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;
- 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,

[1] 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).

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[2]. 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.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[3], 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.

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

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

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[4]).

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.).

[4] www.ema.europa.eu

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[5] and the Template for the Package Leaflet[6]).

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.

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;

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

- 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[7], the Guideline on Summary of Product Characteristics[8] and the Template for the Package Leaflet[9]. 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).

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.

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

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[10]). 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[11]).

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.

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

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