

1 3 March 2022  
2 EMA/608947/2021 - **Draft for public consultation**

3 **Guideline on good pharmacovigilance practices (GVP)**  
4 **Module XVI Addendum III – Pregnancy prevention programme and other**  
5 **pregnancy-specific risk minimisation measures**

Draft finalised by the Agency in collaboration with Member States	9 November 2021
Draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	3 January 2022
Draft adopted by Executive Director	3 March 2022
Release for public consultation	14 March 2022
End of consultation (deadline for comments)	31 May 2022
Anticipated date for coming into effect after finalisation	Q1 2023

6  
7

This new guidance defines the elements of a pregnancy prevention programme and provides for deciding when such programme is needed or other risk minimisation measures are considered appropriate to avoid adverse pregnancy outcomes due to use of medicines and to preserve health of both the mother and the child.

Those participating in the public consultation are asked to submit comments via the EU survey tool linked [here](#).

8  
9  
10

## 11 **XVI.Add.III.1. Introduction**

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

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

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

## 28 **XVI.Add.III.2. Criteria for requiring a PPP or selecting** 29 **pregnancy-specific risk minimisation measures**

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

- 32 • Level of scientific evidence for the teratogenic potential of a medicinal product in humans,  
33 including the evidence on the magnitude and nature of the teratogenic effect; and
- 34 • Context of the likely use of the medicinal product (see also **CHMP Guideline on Risk**  
35 **Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to**  
36 **Labelling<sup>2</sup>**).

37 Both these criteria should be re-assessed regularly.

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

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

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

---

<sup>1</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

<sup>2</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

## 45 **A) Proven or strongly suspected teratogenicity**

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

50 Where the magnitude and nature of the teratogenicity do not justify a PPP (but the first two  
51 criteria are fulfilled), additional pregnancy-specific RMM are considered necessary, in addition to  
52 advice in the summary of product characteristics (SmPC) and package leaflet (PL) as routine RMM  
53 (see CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and  
54 Lactation: From Data to Labelling<sup>3</sup>). As a minimum, these additional pregnancy-specific RMM  
55 should include, usually supported by educational materials for both patients and healthcare  
56 professionals, the following:

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

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

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

## 66 **B) Possible but unconfirmed teratogenicity**

67 If the available evidence suggests possible teratogenicity of a medicinal product, but a causal  
68 relationship between harm in children and the in-utero exposure to the product has not been  
69 confirmed or is not strongly suspected, the decision on whether to require additional pregnancy-  
70 specific RMM in addition to advice in the product information as routine RMM (see CHMP Guideline  
71 on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to  
72 Labelling<sup>4</sup>) should take into account the following considerations:

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

---

<sup>3</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

<sup>4</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

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

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

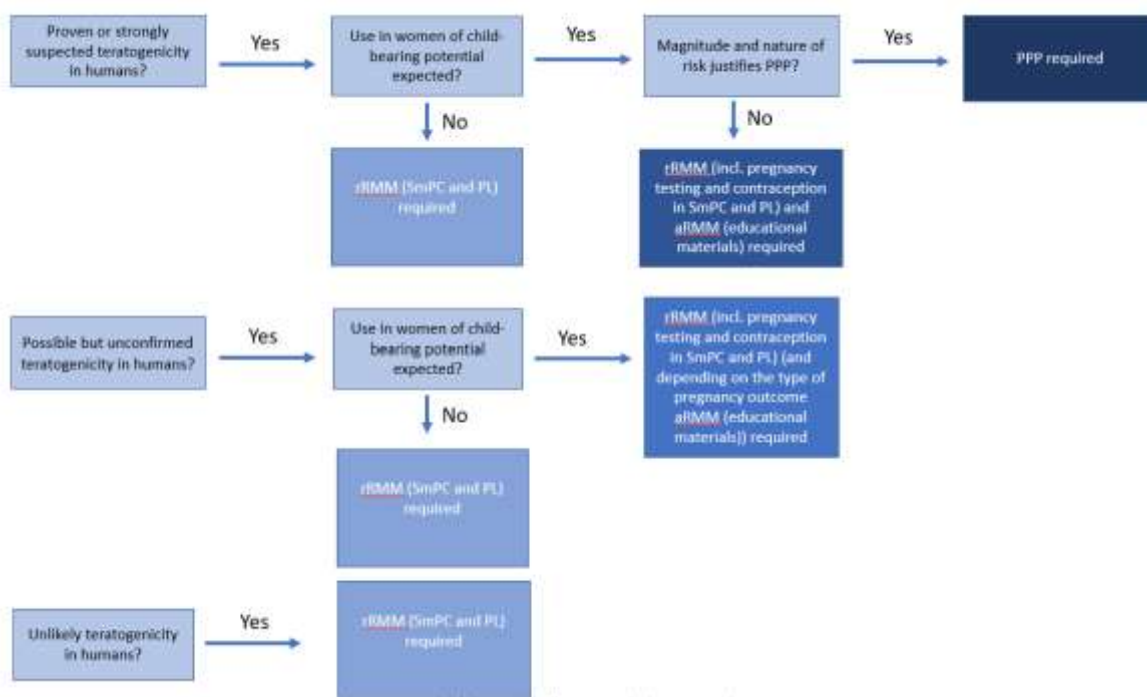
### 81 **C) Unlikely teratogenicity**

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

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

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

90



91

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

94 **XVI.Add.III.3. Risk minimisation measures constituting a**  
95 **PPP**

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

- 99 • Summary of product characteristics (SmPC) and package leaflet (PL) with the following:
- 100 - Contraindication in pregnancy;
  - 101 - Contraindication in women of childbearing potential who are not applying effective  
102 contraceptive measures; and
  - 103 - Information on the teratogenic risks of the product and related recommendations in the  
104 sections on warnings (i.e. SmPC section 4.4 and PL section 2) and on pregnancy (i.e.  
105 SmPC section 4.6 and PL section 2), which may also include criteria defining women who  
106 are not of childbearing potential<sup>5</sup> (see **CHMP Guideline on Risk Assessment of Medicinal**  
107 **Products on Human Reproduction and Lactation: from Data to Labelling**<sup>6</sup>);
- 108 • Required conditions of prescribing (as also defined in the SmPC and PL and referred to in  
109 educational materials) including the following:
- 110 - Before treatment start:
    - 111 ▪ Assessment of the patient’s potential for becoming pregnant and for following the  
112 PPP; and
    - 113 ▪ Personal counselling session of the patient by a healthcare professional on:
      - 114 ○ teratogenic risks of the product;
      - 115 ○ need to avoid pregnancy while using the product and to apply effective  
116 contraceptive measures;
      - 117 ○ importance of discussing with a healthcare professional if the wish for  
118 conceiving a child exists; and
      - 119 ○ time after treatment discontinuation during which pregnancy will also need  
120 to be avoided (where the active substance and/or its metabolites (if  
121 teratogenic) have a long half-life; usually this would be five times the half-  
122 life of the active substance)
  - 123 - At treatment start:
    - 124 ▪ Confirmation of absence of pregnancy through a recent negative pregnancy test,  
125 unless one criterion for considering that the woman is not of childbearing potential  
126 is met (see **Footnote 6**); and
    - 127 ▪ Counselling on effective contraceptive measures
  - 128 - During treatment:

---

<sup>5</sup> 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.

<sup>6</sup> [www.ema.europa.eu](http://www.ema.europa.eu)

- 129                   ▪ Confirmation of absence of pregnancy at an appropriate frequency, normally  
130                   through a negative pregnancy test, unless one criterion for considering that the  
131                   woman is not of childbearing potential (see Footnote 6) is met; and  
132                   ▪ Reminder personal counselling sessions on:  
133                   ○ need to avoid pregnancy while using the product and to apply effective  
134                   contraceptive measures;  
135                   ○ importance of discussing with a healthcare professional if the wish for  
136                   conceiving a child emerges; and  
137                   ○ the reasons why counselling sessions are needed with the frequency  
138                   considered appropriate given the context of product use  
139                   - At treatment end, taking into account the half-life of the active substance and its  
140                   teratogenic metabolites:  
141                   ▪ Confirmation of absence of pregnancy at an appropriate frequency, normally  
142                   through a negative pregnancy test, unless one criterion for considering that the  
143                   woman is not of childbearing potential (see Footnote 6) is met; and  
144                   ▪ Reminder personal counselling session on:  
145                   ○ time period during which pregnancy will also need to be avoided  
146                   • Required conditions of dispensing (as also defined in the SmPC and PL and referred to in  
147                   educational materials), e.g.:  
148                   - Dispensing within a limited number of days after the prescription date;  
149                   - Dispensing a limited quantity of product to ensure that treatment start is aligned with a  
150                   negative pregnancy test (how this is achieved can differ between Member States);  
151                   - Accessibility to the dispenser of the confirmation that the patient has been counselled  
152                   regarding the teratogenic risks and understands the need to avoid product use during  
153                   pregnancy in line with the recommendations from competent authorities in Member  
154                   States;  
155                   - No allowance for free samples of the product;  
156                   • Educational materials targeting healthcare professionals (e.g. in guides, checklists or other  
157                   materials as applicable, see GVP Module XVI) which includes key information on the following:  
158                   - Teratogenic risks of the product;  
159                   - Required pregnancy testing, the required conditions of prescribing and dispensing and the  
160                   required personal counselling of the patient;  
161                   - Need to ensure that effective contraceptive measures are applied; and  
162                   - Guidance on how to act in the case of pregnancy and how to help ensure that any possible  
163                   pregnancy outcomes are evaluated appropriately;  
164                   • Educational materials targeting patients which includes key information on the following:  
165                   - Teratogenic risks of the product;  
166                   - Required actions to avoid use of the product during pregnancy, e.g. applying effective  
167                   contraceptive measures;

- 168 - Need for a negative pregnancy test result to be verified by a healthcare professional before  
169 treatment start and be repeated at suitable intervals during and after treatment if  
170 applicable;
- 171 - Guidance on the need to consult a healthcare professional in the case of pregnancy;
- 172 - Counselling before treatment start and regularly during and after treatment, and also in  
173 the event of a pregnancy (with evaluation of the outcome of any pregnancy); and
- 174 - Handling of any unused product in line with Member States and local procedures to avoid  
175 misuse and accidental exposure (including advice to return unused medicine at the end of  
176 treatment to the physician or pharmacist)

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

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

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

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

190 The format of such a risk awareness form, e.g. electronic in addition to paper-  
191 based materials or recording in the patient's medical record, will depend on what is  
192 most suitable given the context of product use and the applicable legal framework  
193 of each Member State.

194 Further, when requiring a PPP, the following pregnancy-specific RMM should be considered to  
195 become part of the PPP:

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

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

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