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Committee for Medicinal Products for Human Use (CHMP); Pharmacovigilance Risk Assessment Committee (PRAC)

Concept paper on revision of the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling

Agreed by Committee for Medicinal Products for Human Use (CHMP); Pharmacovigilance Risk Assessment Committee (PRAC)	April 2024
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The concept paper proposes to revise the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005)

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1. Introduction

The PRAC and CHMP work plans for 2023 [1,2] list several activities intended to implement guidance on "Special populations and products". This includes further optimising close cooperation between these two Committees for the revision of the 'CHMP Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005)' [3]. This concept paper outlines the areas in this guideline which are planned to be updated. This has been developed by a drafting group involving members from CHMP, PRAC, Non-clinical working party (NcWP), 3Rs working party (3RsWP), Quality review of documents working party (QRD) and Healthcare professionals working party (HCPWP). Representatives from the Patient and consumers working party (PCWP) have been invited and intend to contribute at a later stage of the guideline revision.

The current guideline provides guidance on the integration processes of clinical and non-clinical data for the assessment of the risk of adverse maternal, fetal or child effects in humans, as well as effects on fertility. Further, there is guidance on how to communicate the potential or identified risk through the Summary of Product Characteristics (SmPC).
A decision scheme to determine whether a medicinal product should be contraindicated during pregnancy is also included. Examples of standardized text for the SmPC are given for recommendations on the use during pregnancy and breastfeeding.

Wording regarding pregnancy and breastfeeding included in the SmPC and PL is intended to help healthcare professionals and patients making individual decisions about using a medicinal product during pregnancy and breastfeeding, and actions to take in case of unintended exposure.

2. Problem statement

At time of marketing authorisation, often only non-clinical data is available to provide information on fertility, pregnancy and breastfeeding in the SmPC and PL. The lack of clinical data on medicines safety for human fertility, during pregnancy and breastfeeding has long been highlighted as an area of public health need [4], and patients and healthcare professionals have expressed the need to have access to more information on the safety of medicines during pregnancy and breastfeeding [5].

Currently, the guideline does not provide corresponding standard texts for the Package Leaflet (PL).

In its Regulatory Science Strategy to 2025 [6], the EMA highlights their commitment to advance access through better understanding and communication of benefits, risks, and uncertainties of medicines use in pregnancy and breastfeeding, throughout the product lifecycle.

Most data regarding human pregnancy exposures are collected after marketing authorisation by spontaneously reported post-authorisation data, in patient/pregnancy registries, and via epidemiological studies undertaken in such data sources [7]. Such data sources are available in the EU, as compiled by the European Network of Centres for Excellence in Pharmacovigilance and Pharmacoepidemiology (ENCePP)[1]. The desire to obtain relevant data as early as possible in the product life cycle is being addressed through an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[2] initiative.

Human breastfeeding information in the SmPC and PL often derives from pharmacokinetic evaluations (e.g. bioavailability), from animal studies (e.g. radiolabelled distribution studies) and clinical experience, generally obtained post -authorisation. Human studies on substance transfer into breast milk are still rarely submitted within marketing authorisation applications. The development of

[1] http://www.encepp.eu/structure/documents/Data_sources_for_medicines_in_pregnancy_research.pdf
[2] https://database.ich.org/sites/default/files/ICH_E21_Final_Concept_Paper_2023_1106_MCApproved.pdf

physiologically based pharmacokinetic (PBPK)-modelling approaches may facilitate the prediction of drug exposure in breast milk based on scarce data.

Since the adoption of the guideline in 2008, several developments in the non-clinical field of reproductive toxicology have taken place which have an impact on the interpretation of non-clinical data in relation to use of medicines during pregnancy and breastfeeding. This includes more guidance on interpretation of animal to human exposure margins and the possibility to use new approach methods (NAMs) as alternatives to animals testing, among others [8,9].

3. Discussion (on the problem statement)

The relevance of referring in the revised guideline to the following guidance documents need to be considered:

1. Guideline on good pharmacovigilance practices (GVP) Product- and Population- Specific Considerations Chapter P.III: Pregnant and breastfeeding women (EMA/653036/2019)[3].
2. Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum III – Pregnancy prevention programme and other pregnancy-specific risk minimisation measures (EMA/608947/2021)[4],
3. SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020 corr. 3 in 2022)[5],
4. ICH S5 (R3) Guideline on detection of reproductive and developmental toxicity for human pharmaceuticals[6] (2020), (substitute ICH S5A and S5B).
5. Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95)[7] should be considered and possibly deleted.
6. Non-Clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and Mixed Applications) and in Applications for Simplified Registration (EMEA/HMPC/32116/05 Rev 1)[8]

Considerations to ensure alignment with the relevant guidelines and recommendations

Key adverse pregnancy outcomes

- Teratogenic effects include a range of embryo/fetal adverse outcomes in addition to congenital malformations, such as spontaneous abortion and fetal demise. These could be discussed further since in the current guideline congenital malformations are the only key marker of harm addressed in the risk assessment methodology and classification system.
- Second and third trimester effects. Consideration needs to be given to the possibility of adverse fetal effects arising from exposure *in-utero* beyond the first trimester since the current guideline recommends the assessment of malformative/teratogenic effects, based on the number of first trimester exposed pregnancies. Thus, the current guidance does not detail the possibility of

[3] Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (europa.eu)
[4] GVP Module XVI Addendum III - PPP (europa.eu)
[5] SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (europa.eu)
[6] S5 (R3) Step 5 Toxicity to reproduction (europa.eu)
[7] Guideline on Non-Clinical Documentation for Mixed Marketing Authorisation Applications (europa.eu)
[8] Guideline on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products (europa.eu)

exposure beyond first trimester of pregnancy. More expanded consideration of exposure windows to cover potential risks due to exposure during the entire pregnancy is required.

- Non-clinical considerations: Consideration needs to be given to the interpretation of animal/human exposure margins and the use of NAMs, according to ICHS5(R3). Reporting of animal data in SmPC section 4.6 can be nuanced in certain cases by using the ICHS5(R3) tiered system on how to interpret no observed adverse effect level (NOAEL) for embryo/fetal developmental toxicity testing and an exposure margin based endpoint (>25 fold) above which adverse developmental and reproductive toxicity (DART) findings are considered of minor concern for clinical use. Additionally, the use of NAMs as an alternative to animal testing under certain scenarios and possible weight of evidence building for products within a class of known developmental toxicants based on the pharmacological effect (e.g. anti-PD/L1), may in the near future provide additional human relevant non-clinical information not derived from animal studies. Also, non-clinical developments in assessing exposure via breast milk, and for assessing potential adverse outcomes, should be taken into account.
- Other topics:
    - Long-term child outcomes following exposure during pregnancy, including neurodevelopmental disorders. Update guidance based on current experience.
    - Vaccination of infants after *in-utero* exposure to immunomodulating or immunosuppressive medicines.
    - Multigenerational effects.
    - Embryo/fetal/child risks due to paternal exposure.
- Causality assessment of human reproductive adverse effects. Further description of key elements that may aid causality assessments of signals of reproductive adverse effects should be considered in updating the current guideline.
- Clinical study power. Sample size considerations needed to classify a product risk for congenital malformation should be reviewed, also considering alignment with the 2019 draft GVP guidance (EMA/653036/2019) regarding the definition of risk period and assessment of specific *versus* overall malformation rates.
- Susceptible exposure windows. More detailed information on susceptible periods of exposure should be added to the current guideline, as this is one important factor in assessing teratogenic risk.

Breastfeeding

Currently, there are new methods for estimating levels in breast milk and potential for adverse effects in a breastfed infant, more data leading to better understanding of the risk of medicines for infants exposed via breast milk. The guideline should be updated with current knowledge regarding risk assessment and reflect current views regarding how to communicate about risks in the SmPC and PL, including how to formulate recommendations.

Male and Female Fertility

Although information on risk assessment for male and female fertility is shortly described, there are no standard sentences being provided in the Guideline on the Summary of Product Characteristics[9]. It should be evaluated whether standard texts regarding fertility also should be developed, to cover all different aspects to be addressed in the SmPC section 4.6, and in the PL accordingly.

[9] Guideline on the Summary of Product Characteristics (2005). Rules governing Medicinal products in the European Community Volume 2A and 2B The Notice to Applicants

Standard texts

The terminology of standard statements for use in section 4.6 "Fertility, pregnancy and lactation" of the SmPC, needs to be revised with an aim to improve the information to health care professionals and patients. Furthermore, development of corresponding standard texts for the PL is planned for.

4. Recommendation

The Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) recommends the revision of the current "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" considering the issues identified above.

5. Proposed timetable

Released for consultation in May 2024, deadline for comments July 2024.

6. Resource requirements for preparation

The update of the guideline will involve members of the CHMP, PRAC, NcWP, 3RsWP, HCPWP, QRD, SmPC Advisory Group, EMA Labelling office and EMA pregnancy community. Drafting group meetings will be organised.

7. Impact assessment (anticipated)

The document is intended to provide updated guidance on the integration processes of clinical and non-clinical data for the assessment of the safety of medicines on fertility, in pregnancy and during breastfeeding.

The guideline will provide information on how to communicate potential or identified risks, specifically through the SmPC and PL. This will contribute to address specific information needs for healthcare professionals and patients planning pregnancy, being pregnant, or planning breastfeeding, to promote evidence based informed decisions and support management of diseases during pregnancy and breastfeeding. It will support a harmonised EU position and facilitate consistent recommendations within the pregnancy and breastfeeding related sections of the SmPC and Pl during the life cycle of a medicinal product.

8. Interested parties

The pharmaceutical industry, European learned societies, and scientific organisations (e.g. Innovative Medicines Initiative (IMI), ConcePTION consortium), Academia, HCPs, and patients' organisations. Consultation with other working parties or committees (e.g. CHMP, PRAC, NcWP, 3RsWP, QRD, HCPWP, PCWP) will be initiated as appropriate.

9. References to literature, guidelines, etc.

[1] EMA/PRAC. Pharmacovigilance Risk Assessment Committee (PRAC) Work Plan 2023 (EMA/PRAC/45172/2023). https://www.ema.europa.eu/en/documents/work-programme/prac-work-plan-2023_en.pdf; 2023.

[2] EMA/CHMP. Committee for Medicinal Products for Human Use (CHMP) Work Plan 2023 (EMA/911829/2022). https://www.ema.europa.eu/en/documents/work-programme/chmp-work-plan-2023_en.pdf; 2022.

[3] EMA/CHMP. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf; 2009.

[4] Saint-Raymond A, de Vries CS. Medicine safety in pregnancy and ambitions for the EU medicine regulatory framework. Clinical pharmacology & therapeutics 2016;100(1): 21-3. doi:10.1002/cpt.378.

[5] EMA. Workshop on benefit-risk of medicines used during pregnancy and breastfeeding. https://www.ema.europa.eu/en/events/workshop-benefit-risk-medicines-used-during-pregnancy-breastfeeding. 2020.

[6] EMA. Regulatory science to 2025. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf. 2020.

[7] Sahin, L. & Teil, M. How are prescription medications labeled for pregnancy and lactation? In Teratology Primer 3rd edn. Society for Birth Defects Research and Prevention, Reston, VA. 2018.

[8] ICHS5(R3) Guideline on detection of reproductive and developmental toxicity for human pharmaceuticals (EMA/CHMP/ICH/544278/1998). https://www.ema.europa.eu/en/ich-s5-r3-guideline-detection-reproductive-developmental-toxicity-human-pharmaceuticals-scientific; 2020

[9] Andrews PA, et al. Analysis of exposure margins in developmental toxicity studies for detection of human teratogens. Regul Toxicol Pharmacol. 2019.