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How pharmacovigilance guidelines are addressing this special population

EMA Workshop on benefit-risk of medicines used during pregnancy and breastfeeding

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Regulatory framework

- Absolute benefit/risk balance for single medicinal product
  - Not relative benefit/risk balance
- Product information & risk management planning focussed on specific medicine's characteristics, risk minimisation measures, follow up activities
  - Not disease treatment guidance

Assessment of application for marketing authorisation

- Application with documentation (quality, efficacy, safety, risk management) submitted by company
- Reviewed by assigned Rapporteurs incl one from Pharmacovigilance risk assessment committee (PRAC) (assessor teams at National competent authorities)
- Assessments discussed at EMA Committees (CHMP, PRAC)
  - Questions to company
  - Assessment of responses
- Scientific opinion of approval or rejection
- Decision taken by EU commission
  - Product information
  - Risk management plan (RMP) incl. agreements for further studies, additional risk minimisation measures if needed

Assessment of risks regarding reproduction

Application for approval

- Non-clinical data covering all stages of reproduction; together w. mechanistic data, class effects, and clinical data if available
- Information / recommendations in product information
  - Considering target population, need for treatment etc
- Decisions regarding RMP
  - Pregnancy / reproduction /breast feeding
    - Identified / potential risks ? Missing information ?
  - Need for further specific follow up (pharmacovigilance activities)?
    - Post authorisation studies
  - Need for additional risk minimisation measures (RMM) ?
    - Educational material, others

Assessment of risks regarding reproduction

Post approval

- Routine regular reviews in periodic safety update reports
- Routine signal detection in databases of suspected adverse reactions reported post marketing, literature
- Post approval safety studies based on e.g. registry data addressing e.g.
  - Pregnancy outcomes
  - Effectiveness of risk minimisation activities

➢ Can lead to different regulatory actions

Guidelines on
Good vigilance practices (GVP)

28 July 2017
EMA/873138/2011 Rev 2*

Guideline on good pharmacovigilance practices (GVP)

Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

VI.B.6. Special situations

VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding

Extracts ….

- …. Individual cases with abnormal outcome after pregnancy exposure classified as serious reports ….
- …. Reasonable attempts be made to obtain information on any possible medicinal product exposure to embryo/ fetus; to follow-up on pregnancy outcome…
- …. Signal of possible teratogen effect (e.g. cluster of similar abnormal outcomes) notified immediately to authorities (see in GVP Module IX)

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/653036/2019 DRAFT FOR PUBLIC CONSULTATION
4 December 2019

Guideline on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations III: Pregnant and breastfeeding women

Draft finalised by the Agency in collaboration with Member States	19 November 2019
Draft agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	29 November 2019
Draft adopted by Executive Director	4 December 2019
Release for public consultation	11 December 2019
End of consultation (deadline for comments)	28 February 2020
Anticipated date for coming into effect after finalisation	Q4 2020/Q1 2021

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

Aim to

Minimise adverse outcomes from medicine use during pregnancy, without unnecessarily withholding useful treatment options from pregnant women

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-population-specific-considerations-iii_en.pdf

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Effects on fertility; use of medicines in neonates out of scope

P.III.B.4 Post-authorisation safety studies PASS

Consider PASS when use expected in pregnancy e.g.

- product cannot be discontinued due to disease, disorder arising in pregnancy, if changes in treatment during pregnancy associated with risks for pregnant woman and/or foetus;
- non-clinical/ clinical signal, properties indicate potential risk in pregnancy
- medicine used for conditions common in women of child-bearing potential
- measure compliance (effectiveness) with risk minimisation measures

Further data collection when concerns lead to strict label (avoid use in pregnancy) ?

P.III.B.4 PASS – Study types

- PK – address pregnancy related physiological conditions
- DUS : descriptive studies on use patterns
- Drug safety studies w. pharmacoepidemiological methodology
  - Epi-studies preferably in existing data sources
    - Further details on methodology, pregnancy registries etc
- Studies on effectiveness / impact of RMM
- Assessing long-term effects of medicine use in pregnancy
  - Challenging; multidisciplinary approach

PIII.B7 Risk minimisation measures

Objective

Reduce risk to child as much as possible vs need for treatment for mother

- E.g. : avoid inadvertent in utero exposure; modify medication before /during pregnancy; mitigate risk at unplanned pregnancy (discontinue / switch ?; intensified monitoring)

Measures

- Risk proportionate: from relevant information & open recommendation to very strict measures as Pregnancy Prevention Program (e.g. known teratogenic medicine needed to be used by women of child bearing potential)
- Educational materials for health care professionals a/o patients
- Advice on contraception
- Effectiveness of PPP – if pregnancy occurs, root cause analysed & reported

PIII.B6 Safety communications

Communication objectives

Enable women & HCPs taking informed decisions to e.g. prevent negative impact on child; unnecessary pregnancy termination, promoting RMM

Issues to address in communication materials (PI, aRMM) e.g.

- Characterisation of adverse pregnancy risks (ideally e.g. dose, duration, timing etc)
- Magnitude of absolute risk for birth/developmental defect + absolute number of background prevalence
- Additional RMM, including PPP and contraception advice;

Communication tailored for e.g. women/adolescent female patients & partners, parents or carers, HCPs

Challenges

Minimise adverse outcomes from medicine use during pregnancy, without unnecessarily withholding useful treatment options from pregnant

If concerns (e.g. non-clinical, class effects) lead to strict label (avoid use in pregnancy) – what type of follow up activites relevant ?

Effective risk minimisation measures and communication

BACK UP

Appendix 2: Pregnancy testing, contraception for pregnancy prevention during treatment with medicines of teratogenic potential

- Risk of pregnancy should be assessed prior to each teratogen prescription
- Risk of pregnancy may be high at start of method or when switching between methods due to unprotected sex prior to starting the method, unreliable use of previous method, time needed to establish contraceptive efficacy of new method
- Pregnancy tests at start of contraceptive method may not detect an early pregnancy following unprotected sex in last three weeks. Any starter on new method should have a repeat pregnancy test at 3 weeks if there is any risk of pregnancy at start of contraceptive method
- Duration of teratogen prescriptions may need to be shortened for patients who use contraceptive methods that require frequent pregnancy testing.

Effectiveness of contraceptive in typical use[1]	Contraceptive method	Duration contraceptive method used / other situations	Pregnancy test needed before next teratogen prescription?
Highly effective methods **(Typical use failure rates less than 1%)**	Copper intrauterine device (copper IUD)	Established user more than 3 weeks to 5-10 years (depending on IUD[2])	No
	Levonorgestrel-releasing intrauterine system (LNG-IUS)	Established user more than 3 weeks to 3-5 years (depending on IUS[2])	No
	Progestogen Implant	Established user more than 3 weeks to 3years	No
		Established user (more than 3 weeks), but concurrent use of interacting medicines which may affect efficacy[3]	Yes + review / refer for contraceptive advice
Effective methods **(Typical use failure rates greater than 1%)** **Additional barrier**	Depot medroxyprogesterone acetate (DMPA) subcutaneous (SC) or intramuscular (IM) injections[4]	Established user (more than 3 weeks + repeat injections on schedule) and less than 13 weeks since last injection + documented as administered by healthcare professionals	No
		Established user (more than 3 weeks + repeat injections on schedule and less than 13 weeks since last injection) but self-administered or undocumented administration	Yes, test if any suspected risk of pregnancy
		More than 13 weeks since last injection (i.e. beyond recommended duration of use of last injection)	Yes + review / refer for contraceptive advice

Additional barrier methods are advised during teratogen use		beyond recommended duration of use of last injection)	+ review / refer for contraceptive advice
	Combined hormonal contraceptives (pills, patches or vaginal ring) or progestogen-only pills	Established user (more than 3 weeks), reliable and consistent use	Yes, test if any suspected risk of pregnancy
		Established user (more than 3 weeks) but with unreliable or inconsistent use of method, eg: • missed pills, late patch • Diarrhoea or vomiting; • use of other interacting medicines that may affect efficacy[3]	Yes + review / refer for contraceptive advice
	Other methods or no contraception	Any duration of use of other methods	Yes + review / refer for contraceptive advice;
		No contraception	Assess need for contraception + test if any suspected risk of pregnancy + review / refer for contraceptive advice;

1. Effectiveness of methods based on failure rates in typical use rather than perfect use. Perfect use failure rates similar for specific methods listed (0.03 – 0.6%); risk of user error higher for daily methods than long acting reversible contraceptive methods; highest for methods used at time of sexual intercourse. Highly effective methods based on less than 1% failure rate in typical use; Less effective methods greater than 1% failure rate (6 – 9%) in typical use (Trussell J 2011 May;83(5):397-404. doi: 10.1016/j.contraception.2011.01.021. Epub 2011 Mar12).
2. Refer to PI for specific products; patients should be reviewed / referred for contraception advice at end of the recommended duration of use.
3. Implants only considered as highly effective; combined hormonal contraceptives, progesterone-only pills only effective if interactions with any concurrent medicine not concern (see FSRH Guidance...).
4. DMPA (IM or SC) injection can be considered as highly effective if administered by HCPs & continuous repeat use documented as occurring within recommended duration of action (= perfect use, failure rate = 0.2%). Otherwise considered an effective contraceptive (typical use failure rate =6%). Same rationale be used for other injection products with different recommended duration of action (e.g. Norethisterone enanthate).

P.III.A.1.4. Adverse events in child after exposure through breast milk

Adverse events in child following exposure through breastfeeding

- Adverse events after exposure through breastfeeding identified so far mostly immediate effects on child (e.g. sedation, irritation, gastro-intestinal disturbances).
- Kinetics (long half-life - risk of accumulation; maternal intake (single, few doses, chronic, treatment during pregnancy etc)
- PK data in breast milk; PK data in child after intake via breast milk