EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Section 4.6: Fertility, pregnancy and lactation

SmPC training presentation

Note: for full information refer to the European Commission's Guideline on summary of product characteristics (SmPC)

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I. General objectives of section 4.6

Information on the use of a medicine in relation to reproduction refers to a number of aspects (fertility, pregnancy, breastfeeding, health of the foetus, child and mother)

All available knowledge from pharmacological data, non-clinical studies, clinical data and therapeutic practice should be taken into account

Practical recommendations should be made, providing reasons for such recommendations to facilitate healthcare professionals' information to the patient

Efforts should be made to update the recommendations on the basis of human experience in exposed pregnancies which may supersede initial non-clinical data

If appropriate, cross reference should be added to section 4.3 (in case of contraindication), 4.4 (e.g. when contraceptives measures are required), 4.5 (if interaction with contraceptives), 4.8 or 5.1 (details of clinical data), or, 5.3 (details of non clinical data)

Section 4.6 should therefore be reviewed with due consideration to the CHMP Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling and the standard statements included in its Appendix 3

II. 1 Pregnancy

Conclusions of non-clinical reproductive toxicity
(details to be provided in Section 5.3)

Comprehensive information on human data/Extent of the human experience

Recommendations on the use in women of childbearing potential and on contraceptive measures (in males and females), *when appropriate*

Recommendations on the use of the medicine during different periods of gestation

+/- Recommendations on the management of exposure during pregnancy when appropriate, including relevant specific fetal or neonatal monitoring

Standard statements
SmPC examples
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With respect to pregnancy, appendix 3 has to be read in conjunction with the "Integration table for risk assessment and recommendation for use" presented in Appendix 1 of the same guideline

II.2 Breastfeeding

Clinical data:
- Conclusions of kinetic studies (e.g. transfer into milk)
- If available, information on adverse reactions in nursing neonates

Only if there is no human data, conclusions from non-clinical studies on the transfer into milk

Recommendations should be given:
- To stop or continue breastfeeding

and/or

- To stop or continue the treatment

SmPC examples
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II.3 Fertility

The main information on the possible effects of the medicinal product on fertility (male and female) must be included in section 4.6

Clinical data and relevant conclusions from non-clinical toxicity studies, if available

Recommendation for use of the medicinal product when pregnancy is planned but fertility might be affected by treatment should be included

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If there are no fertility data at all, this should be stated

Example 1–pregnancy-contraindication

Active substance X 200mg hard capsules

The use of active substance X is contraindicated during pregnancy.

Preclinical data:
- Fertility: In animal studies, active substance X produced reversible effects on spermatogenesis (see section 5.3).
- Teratogenicity: Significant teratogenic and/or embryocidal potential have been demonstrated for active substance X in all animal species in which adequate studies have been conducted, occurring at doses as low as one twentieth of the recommended human dose (see section 5.3).
-Genotoxicity: active substance X induces genotoxicity (see section 5.3).

Female patients: Active substance X must not be used by females who are pregnant (see sections 4.3 and 5.3). Extreme care must be taken to avoid pregnancy in female patients (see section 5.3). Therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for four months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time. If pregnancy does occur during treatment or within four months from stopping treatment, the patient must be advised of the significant teratogenic risk of active substance X to the foetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking active substance X (see sections 4.3, and 5.3). Active substance X accumulates intracellularly and is cleared from the body very slowly. It is unknown whether the active substance X that is contained in sperm will exert its potential teratogenic or genotoxic effects on the human embryo/foetus. Although data on approximately 300 prospectively followed pregnancies with paternal exposure to active substance X have not shown an increased risk of malformation compared to the general population, nor any specific pattern of malformation, male patients and their female partners of childbearing age must be advised to each use an effective contraceptive during treatment with active substance X and for seven months after treatment.
Men whose partners are pregnant must be instructed to use a condom to minimise delivery of active substance X to the partner.

Example 2–pregnancy-contraindication

Active substance X 10 mg film-coated tablets

There are no adequate data from the use of active substance X in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that active substance X passes the placenta, active substance X is contraindicated during pregnancy (see section 4.3).

Example 3–pregnancy-contraindication

Active substance X 16mg tablets

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.
Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Example 4–pregnancy-contraindication

Active substance X 20mg hard capsules

Pregnancy
There is insufficient data on the use of active substance X during pregnancy.
Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women.

Therefore, active substance X is contraindicated during pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception.
If a patient becomes pregnant while taking active substance X, therapy should be discontinued.

Example 5–pregnancy

Active substance X 20mg hard capsules

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of active substance X on pregnancy or on the health of the foetus/newborn child. Active substance X can be used during pregnancy.

Example 6–pregnancy

Antipsychotics (conventional and atypical) and use during the third trimester of pregnancy and risk of abnormal muscle movements and/or withdrawal symptoms in newborns warning

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Neonates exposed to antipsychotics (including [NAME]) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Example 7–breastfeeding

Active substance XY 2.5mg/120 mg modified-release tablets

Active substance X and Y are both excreted in breast milk. Decreased milk production in nursing mothers has been reported with active substance Y. Therefore active substance XY should not be used in breastfeeding women

Example 8–breastfeeding

Active substance X 375 mg film-coated tablets

Breast-feeding Active substance X and its major metabolite are excreted in rat milk (see section 5.3). It is not known whether active substance X is excreted in human breast milk. Because of the potential for adverse reactions in breastfed infants, due to the combined treatment of active substance X with peginterferon alfa and ribavirin, breast-feeding must be discontinued prior to initiation of therapy.

Example 9–breastfeeding

Active substance X 0.31 mg, powder for solution for injection

Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast feeding should be interrupted and the expressed feeds discarded. It is usual to advise that breast feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv. Due to the short six-hour, half-life of 99mTc, a dose of less than 1 mSv in mother's milk can be expected 24 hours after the administration of active substance X [99mTc].

Example 10–breastfeeding

Active substance X, suspension for injection

In breastfeeding mothers given active substance X or placebo during the vaccination period of the clinical trials the rates of adverse reactions in the mother and the breastfed infant were comparable between the vaccination and the placebo groups.
In addition, vaccine immunogenicity was comparable among breastfeeding mothers and women who did not breastfeed during the vaccine administration. Therefore active substance X can be given to breastfeeding women.

Example 11–breastfeeding

Active substance XYZ 600 mg/200 mg/245 mg film-coated tablets

Lactation: studies in rats have demonstrated that active substance X and Z are excreted in milk; concentrations of active substance X were much higher than those in maternal plasma. It is not known whether active substance X, Y or Z are excreted in human milk. Because of the potential for both HIV transmission and the potential for serious undesirable effects in breast feeding infants, mothers should be instructed not to breast-feed if they are receiving active substance XYZ.

Example 12–fertility

Active substance X 100 mg tablets

No human data on the effect of active substance X on fertility are available. In rats, there was no effect on mating or fertility with active substance X treatment (see section 5.3).

Example 13–fertility

Active substance X 5 mg/ml powder for suspension for infusion

Active substance X induced infertility in male rats (see section 5.3).
Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with active substance X.
Sexually active men and women should use effective methods of contraception during treatment and up to six months after treatment for men, and one month after treatment for women.

Example 14–fertility

Active substance X 20 mg/ml concentrate for solution for infusion

Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys (see section 5.3). Active substance X may impact the ability of a woman to become pregnant.

Example 15–fertility

Active substance X 25 mg/ml powder for suspension for injection

There are no human data on the effect of active substance X on fertility. In animals, adverse effects of active substance X on male fertility have been documented (see section 5.3). Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. Before starting treatment, male patients should be advised to seek counselling on sperm storage.

III. FAQs

1. Can a reference to a specific program to monitor outcomes of pregnant women exposed to a medicinal product be included in the SmPC?

2. Where should information regarding pregnancy prevention programme be placed in the SmPC?

1. Can a reference to a specific programme to monitor outcomes of pregnant women exposed to a medicinal product be included in the SmPC?

- The SmPC should inform on the risk minimisation measures to be taken when there is a potential reproductive toxicity and provide recommendations on the use or not of the product during gestation and the (clinical) management of exposure during pregnancy. Information on a specific programme will be better included in educational material of a risk management plan (RMP)

2. Where should information regarding pregnancy prevention programme be placed in the SmPC?

- The conditions, in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled, in particular, specific risk minimisation measures requested as part of a risk management plan to ensure safe and effective use should be provided in section 4.4. Therefore, the measures to be taken as part of the pregnancy prevention programme should be described in section 4.4
- Section 4.6 should provide complementary information on the reasons for the recommendation of a pregnancy prevention programme

Thank you for consulting this training presentation

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Please note the presentation includes examples that may have been modified to best illustrate the related principle