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GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

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EXECUTIVE SUMMARY

Integration of animal and human data to assess the risks of the use of medicinal products during pregnancy is a critical task, which is aimed at reducing the induction of birth defects as far as possible. In this document the process of assessment of non-clinical, i.e. animal data is described, followed by guidance on the assessment of human data.

Integration of these assessments is essential for the labelling of a medicinal product. A decision scheme is provided to determine whether or not a contraindication during pregnancy should be settled in the labelling.

Examples of standardized texts are given for recommendations on the use during pregnancy and lactation.

1 INTRODUCTION AND BACKGROUND

The information and advice given on how to use a medicinal product in relation to human reproduction should allow a physician to manage a number of situations. These situations include prescription of medicinal products to women of child-bearing potential, pregnant or breast-feeding women. Therefore information on the risks following exposure to the medicinal product before and during pregnancy, and during lactation should be provided as well as recommendations on the management of risk in clinical practice.

The risk assessment is based on an integrated evaluation of non-clinical and clinical data, which includes consideration of non-clinical pharmacological and pharmacokinetic properties of the medicinal product, as well as results from non-clinical toxicity studies and of clinical experience. During drug development, and early post marketing period, non-clinical data are of greater importance since clinical experience is still lacking or limited. The clinical data becomes more important as experience grows.

For both non-clinical and clinical data, the assessment should take into account the methodology for data collection, as well as the quality of the data. To allow a proper evaluation (*i.e.* assess the relevance of findings), the available studies must be of adequate scientific quality.

2 PURPOSE OF THE GUIDELINE

The purpose of this guideline is to:

- Describe the integration processes of non-clinical and clinical data and highlight the factors of importance for the assessment of the risk of an adverse reproductive/developmental effect in humans (fertility, pregnancy, health of the foetus and child), based on the assessment of reproductive toxicity studies in animals and human clinical data,

- Outline how to communicate the potential or identified risk. Information and recommendations on how to use the medicinal product are addressed in the Summary of Product Characteristics (SPC) of the medicinal product, taking into account the nature of the risk.

3 SCOPE

This guideline applies to medicinal products for human use.

4 LEGAL BASIS

This guideline is based on the Directive 2001/83/EC, as amended. With respect to non-clinical data, the guideline refers primarily to the ICH guidelines on Reproductive Toxicity: Reproductive toxicology: Detection of Toxicity to Reproduction for Medicinal Products Including Toxicity to male fertility (ICH S5A [CPMP/ICH/386/95] and ICH S5B [CPMP/ICH/136/95]), and Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies (ICH S3A [CPMP/ICH/384/95]).

With respect to mixed applications reference should be made to the guideline on the "Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95)" and to the Guideline on "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)"

The need for clinical data should be considered in line with the Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005).

5 NON-CLINICAL ASSESSMENT

The non-clinical assessment should be based on the reproductive toxicity studies and all pharmacological (primary, secondary and safety) and all toxicological data available. Repeated dose toxicity studies can provide important information regarding potential effects on reproduction, particularly male fertility.

The aim of the reproductive toxicity studies is to reveal any effect of a medicinal product on mammalian reproduction.

Reproductive toxicity includes:

- Effects on reproduction in the parental generation: any effects on the male and or female reproductive organs or the related endocrine systems including gamete production and transport, reproductive cycle, sexual behaviour, fertility, gestation, parturition, pregnancy outcomes, lactation, or modification of other functions that are dependent on the integrity of the reproductive system

- Developmental toxicity: any adverse effect induced in the progeny. This includes effects induced or manifested in the embryonic or foetal period (adverse effect on the conceptus resulting from prenatal exposure) and those induced during the lactation period or manifested postnatally (adverse effect on e.g. behaviour and sexual maturation).

The following points are important and should be taken into consideration:

- Choice of species

The rat is usually used in all reproductive toxicity studies, whereas the rabbit is usually the second species in the embryo-foetal toxicity study. In cases where the rat or rabbit were considered unsuitable for testing by the applicant, an alternative rodent or non-rodent species should have been considered. In exceptional cases, a second rodent species may be acceptable in embryotoxicity studies, instead of a non-rodent species.

At least one of the selected species should be responsive to the primary pharmacodynamic effect of the medicinal product. Where this has not been possible, the impact of this deficiency should be addressed in the non-clinical overview of the Common Technical Document.

- Pharmacokinetics:

The pharmacokinetic profile including biotransformation should enable an extrapolation of the results from animals to humans, and to assess the relevance of the species selected for testing.

For herbal preparations kinetic data should be submitted only if toxicologically relevant constituents have been identified.

Information regarding placental transfer and excretion into milk of the medicinal product and/or its metabolites would be of value for the assessment.

- Route of administration:

The route of administration should be the route intended for human use. An alternative route may be acceptable if a similar or 'better' pharmacokinetic profile (i.e. resulting in higher exposure) can be demonstrated.

- Dose in the reproductive toxicity studies:

The dose range tested by the applicant should have covered a dose resulting in minimal maternal toxicity such as e.g. decreased body weight or food consumption. Whilst it is desirable that a "no observed adverse effect level"(NOAEL) has been determined, it is more important that dose intervals

have been close enough to reveal any dose-related trends. If excessive dose intervals have been used there is a risk of missing any teratogenic potential and the study may be rated as insufficient.

In developmental toxicity studies, doses causing severe maternal toxicity are not possible to evaluate, since embryofetal adverse effects could be a direct consequence of the medicinal product or secondary to the poor maternal condition.

- Toxicokinetics:

The exposure in pregnant animals of the compound and/or metabolites should be assessed

- Mechanism:

If reproductive toxicity has been identified, information on the mechanism is desirable.

Evaluation process

5.1 Deficiencies in available data

If no non-clinical studies were conducted or if some non-clinical studies are lacking, or some studies are irrelevant, or if data on certain endpoints are lacking, the impact of insufficient data should be addressed in the evaluation and the lack of data should be justified.

5.2 No effect detected

If adequately designed reproductive studies with adequate systemic exposure do not indicate direct or indirect harmful effects, and there are no relevant effects identified in other pharmacological or toxicological studies, this should be stated to enable the finalisation of the evaluation process.

If there is a class effect expected, and no findings are observed, this may need further investigation.

5.3 Effects detected

If an effect suggesting reproductive toxicity was detected (e.g. a finding in a reproductive toxicity study or toxicity to a reproductive tissue and /or system, or a behavioural effect, observed in a toxicology and/or safety pharmacology study), the evaluation process should continue as outlined below in order to assess the level of concern.

There are several contributory elements that may affect the level of concern. The following aspects should be taken into consideration:

General aspects:

- Recognition of an effect

Statistically significant differences alone should not necessarily constitute a positive signal. Other criteria of importance include biological plausibility, reproducibility, medicinal product- or species-specific mode of action, relationship to an animal-specific metabolite, and/or clear dose-response relationship.

- Cross-species concordance:

If the same effect is observed in more than one species, it may increase the concern for reproductive toxicity in humans. Cross-species concordance is most likely to be identified for structural changes or developmental mortality because these endpoints are studied in multiple species.

- Type of effects:

Morphological effects have more weight in estimating the concern for reproductive toxicity in humans, than general effects (e.g. growth retardation). The latter, possibly a reversible effect, might be induced by maternal stress or other maternal toxicity.

- Multiplicity of effects

Multiplicity of effects usually increases concern for reproductive toxicity in humans. Multiplicity refers to the observation, in a single species or animal model, of two or more effects with related biological endpoints, e.g. on foetal examination, abnormal shaped vertebrae plus abnormal number of

vertebrae would give rise to increased concern, more than just a single observation with regards to vertebral development.

- Adverse effects at various stages of the reproductive process:

This refers to observations in a single species or animal model, of effects during different stages of the reproductive process, e.g. increased early intrauterine death plus some cardiac malformations would give rise to increased concern with regards to developmental toxicity.

- Additional information

Information from other sources may influence the level of concern, e.g. adverse signals from non-clinical studies using transgenic animals.

- Rare event:

Reproductive toxicity studies usually lack the statistical power to detect subtle increases in rare events. Thus, an increased frequency of rare events in exposed animals may increase the concern for reproductive toxicity in humans. Rare events need not be mentioned in the SPC, but should be mentioned in the risk-management plan as they may lead to a signal.

Specific aspects:

- Data from reproductive toxicity studies and/or from repeated dose toxicity studies may suggest detrimental effects on fertility. In repeated dose toxicity studies, such effects could be alterations to endocrine function or histopathological changes in the gonads or genital organs, which may be detected in both rodents and non-rodents.

- Maternal toxicity: the magnitude and nature of the maternal toxicity should be considered when drawing a conclusion about its relevance to the effects observed in the offspring.

- Dose response relationship: when the intensity of any effect is increased with the dose, the concern may be increased.

- Reproductive toxicology linked to pharmacological effect: interspecies comparisons of the pharmacological effect of the compound should be assessed.

- Comparison of the toxic and pharmacodynamic effective dosages:

  The aim is to identify the extent to which there is an overlap between pharmacologically active doses and doses that cause reproductive or developmental toxicity (i.e. the therapeutic window), preferably in the same species. Estimation could be made by the following ratio:

  ➢ Systemic exposure measured at the NOAEL for reproductive toxicity / systemic exposure measured at the pharmacological dose.
  ➢ A biomarker / surrogate marker to determine the NOAEL can be used, which is relevant and possible to determine in animals.

- Animal to human exposure ratio:

  This should be based on the systemic exposure of the animal at the NOAEL for reproductive toxicity and the systemic exposure of human at the maximum therapeutic dose, taking into account the therapeutic window described above

- Recent historical control data from the same strain and preferably from the laboratory in which the study was performed.

5.4 Class alert

A class alert should be based on adverse reproductive effects previously demonstrated in humans by closely related chemical/ pharmacological entities (e.g. retinoids, ACE-inhibitors).

6 CLINICAL ASSESSMENT

The clinical assessment in general will be based on various types of clinical data. These could include case-reports, case series, epidemiological studies, etc. and originate from different sources, e.g.

pregnancy registries, registries of congenital malformations, teratogenic effects networks and pharmaceutical companies, and other types of bibliographical data.

The Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data, EMEA/CHMP/313666/2005 gives detailed information and should be taken into consideration for assessment.

The assessment should take into account the methodology, including the quality of data, the existence of a non-exposed group or control group, the type of controls, and if possible, the inclusion of foetuses aborted due to malformation, etc.

To allow a proper evaluation (i.e. assess the relevance), the available clinical studies must be of adequate scientific quality.

If there are sufficient relevant clinical data, the assessment should be based on these data alone, without taking into account existing results in animals.

6.1   Effects on Male and Female Fertility

Fertility is defined as "the actual reproductive performance of an individual, a couple, a group, or a population", and thus the failure to reproduce defines infertility. Clinical attention is generally restricted to couples who have experienced unprotected intercourse for at least one year, which has not resulted in a conception. There are a variety of parameters that can be affected by a medicinal product, which may result in impaired fertility. The characteristics of the medicinal product, as identified in the non-clinical studies and / or due to the pharmacological profile, as well as the population intended for treatment, will affect how best to undertake an assessment of adverse effects on fertility. Evaluation of both male and female fertility may include but are not limited to, effects on hypothalamic / pituitary gonadal function, as well as effects on the reproductive organs/tissues. In addition, increased early spontaneous abortion, and impairment of implantation are other relevant parameters. A number of surrogate variables may be appropriate, and should be studied on a case-by-case basis. To study effects on fertility by monitoring reproductive outcome in couples is generally not considered feasible.

6.2   Developmental effects:

The administration of a medicinal product during pregnancy may produce various types of effects on the (unborn) child, including death, depending on the period of interference with the developmental phase:

a) A teratogenic (malformative) effect, associated with exposure at the beginning of pregnancy (the first trimester of pregnancy is the period of highest risk), which could also result in embryonic loss.

b) A fetotoxic effect, which includes effects such as growth retardation or adverse effects on either histological or functional maturation of organs (the period of highest risk begins during the second trimester of pregnancy and continues throughout pregnancy).

c) A pharmacological effect in the neonate, which is mostly associated with exposure at the end of pregnancy or during labour.

It needs to be kept in mind that some effects on the newborn child may not be detectable until later in life (e.g. behavioural effects).

In addition there are some rare effects, which do not belong to these "groups" (e.g. transplacental carcinogenesis of diethylstilboestrol (DES)).

6.2.1 Assessment of malformative effects:

The overall incidence of malformations generally detected at birth is approximately 3% of all live births, where these data are available. Each individual type of malformations is uncommon or rare.

A small number of exposed pregnancies may in some instances be sufficient to generate a signal, and depending on the effects found, even be sufficient to conclude on an increased risk.

6.2.1.1 No evidence for an increased frequency of overall number of malformations

Evidence for a no-increased frequency of malformations is unlikely to be provided statistically. Depending on the number of first trimester-exposed pregnancies with known outcomes, different levels of certainty can be reached.

Theoretically, in a clinical trial with a defined control group and strict criteria for definition of the study population, standard power calculations considering the incidence of the endpoint(s) of interest, are used to estimate the size of the trial. Clinical trials in the first trimester of pregnancy to address the risk for the developing embryo and foetus are not conducted. Therefore, risk assessments rely on analyses of already exposed pregnancies (case reports, series, studies…). Thus, the criteria for calculation of samples size required in clinical trials cannot be strictly applied to the pregnancy situation.

It is desirable to identify a relevant control group, to allow for a higher level of certainty for the risk assessment. However, it has to be acknowledged that it is not always possible to find such a group. Given that the frequency of malformations in the general population is relatively well known, uncontrolled data are also of value. When there are reasons to believe that the maternal disease (or other confounders, if present) may have an influence on the frequency of malformations, independently of the treatment, data from a control group is required for interpretation of the data (e.g. pregnant women with untreated illness, or when it applies, those exposed to alternative treatments during pregnancy).

To reflect the specificities of pregnancy data, in the following calculations an overall incidence of birth defects of 3% has been used to derive the numbers of first trimester pregnancies (exposed to a medicinal product) needed to exclude a certain level of risk.

The number of prospectively collected pregnancies required to exclude the specific risks described below ($\geq$2-fold or $\geq$10-fold increase in overall incidence of malformations) have been inflated based on the known difficulties with the accurate documentation and validation of cases. A particular conclusion on the increase in overall incidence of malformations may be substantiated based on fewer first trimester exposed prospectively collected pregnancies only if the complete documentation and validation of the exposed pregnancies can be unequivocally established and the conclusion is statistically valid.

- If no increased incidence of malformations is observed within at least 300 first trimester exposed prospectively collected pregnancies (a moderate amount), with known pregnancy outcomes (births or fetopathological examinations) the conclusion might be reached that the medicinal product at hand is not responsible for a 10-fold or more increase of the overall incidence of malformations.

- If no increased incidence of malformations is observed within at least 1000 first trimester exposed prospectively collected pregnancies (a large amount of data) with known pregnancy outcomes (births or fetopathological examinations), the conclusion might be reached that the medicinal product at hand is not responsible for a 2-fold or more increase of the overall incidence of malformations.

6.2.1.2 A suggested or suspected malformative effect is based on:

- Several relevant case-reports (see statement above) involving the medicinal product. Causal relationship between the medicinal product and the malformation is possible but is not clearly established: plausible chronology, low frequency of the malformation in the general population, specific malformative pattern, etc.

  OR
- Studies in humans suggesting an increase in the overall frequency of malformations or of a specific type of malformation. The relevance of the methodology of each study is reviewed before deciding whether to take the results into account or not. The causal relationship between the medicinal product and the malformation should be further investigated.

6.2.1.3 A **demonstrated** malformative effect is defined when:

- There is clear evidence that a medicinal product is associated with an increase of malformations. This conclusion may only be drawn over time, based on signals that are subsequently confirmed.

- If only case reports are available without further confirmation in a study, there is a need for scientific agreement between experts in the field before such a signal should be included in the risk assessment approach.

6.2.2 Assessment of foetal and/or neonatal toxicity:

An approach similar to that given for the assessment of malformative risk can be used for the assessment of foetal and/or neonatal toxicity for second, third trimester or prepartum exposures.

A difficulty might arise because baseline rates of all neonatal events are not known in the general population. When studying neonatal events where the baseline incidence is unknown, a control group is required to establish a risk. If there are only case reports available, they must be convincing (mechanism of action, toxicological profile, chronological plausibility…).

7   LACTATION

Risk assessment during lactation relies on the detailed analysis of available data:

Major elements of assessment:

- Breastfed infants' plasma concentrations of the medicinal product

- Estimation of the amount of medicinal product received by infants via milk, based on the concentration of the active substance /metabolites in human milk

- Case reports of adverse effect in breastfed infants

- Follow up of breastfed infants during treatment

Complementary data for assessment

- Pharmacokinetics, pharmacodynamics and toxicity profile of medicinal product

- Use and tolerance of the medicinal product in paediatrics

- Known use of the medicinal product during breastfeeding without proper follow up of children

- Non-clinical data:

  ➢   Transfer of the medicinal product in animal milk

  ➢   Peri and post natal studies including survey of offspring during nursing period.

Pharmacological class alert might not be relevant for lactation, i.e. within a class, infant exposure may greatly vary according to the pharmacokinetic properties of each medicinal product, leading to differences in level of risk.

Clinical data, when available, supersedes non-clinical data and should provide the basis of the assessment of the benefit in relation to possible risks of continuing treatment during breast-feeding. If no human data on breast-feeding are available, the risk assessment and the recommendation for use can only be based on non-clinical data

Some herbal products (containing only constituents commonly used in food) may be used without any risen concern. For other comparable products, although apparently excreted without any risk for the child, children are known to refuse breast milk drinking because of induction of an unusual taste. This type of data should be documented at least by bibliography.

Direct risks for the newborn, when there is topical application (e.g. essential oils or allergenic substances) on the breast should be considered.

Data leading to different levels of risks during lactation:

a)   Risk can be established: if effects in breastfed infants are concordant with the pharmacodynamics and/or toxicity profile of the medicinal product, especially if the medicinal product is present in infants' blood.

b)   Risk potentially exists due to a hazardous safety profile: presence of active substance /metabolites in plasma/blood in nursing infants, or fair amount in milk, or absence of clinical data from breastfed infants, but the general safety profile raises concern.

c)   Risk cannot be ruled out: no human data and/or only documented medicinal product transfer into milk from non-clinical data.

d)   No risk is anticipated.

8   INTEGRATION: FROM DATA TO LABELLING

8.1   General principles

Efforts should be made by the applicant to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential. This information is important for the health care professional informing the patient (physician, pharmacist, midwife).

In the overall assessment, all available knowledge should be taken into account, including pharmacological activity, results from non-clinical studies, and knowledge about compounds within the same class.

Aspects such as therapeutic benefit compared with options available, therapeutic alternatives, clinical practices, pharmacokinetics, extraction procedure of herbal medicinal products, information from bibliographic sources etc. should be considered.

Efforts should be made to update the recommendations for use during pregnancy and lactation on the basis of increasing human experience in exposed pregnancies which eventually supersede the animal data.

8.1.1 Fertility

The main information on the possible effects of the medicinal product on fertility must be included in Section 4.6 of the SPC.

This section should include:

a) Clinical data if available

b) Relevant conclusions from non-clinical toxicity studies if available. Further details should be included in Section 5.3 of the SPC.

c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.

Cross-references could be included in Section 4.3 of the SPC, if appropriate.

If there are no fertility data at all, then this should be clearly stated in Section 4.6 of the SPC.

8.1.2 Pregnancy

An integrated approach in risk assessment and recommendations for labelling based on non-clinical and clinical data is presented schematically in Table 1 in appendix 1. Suggestions for wording are provided in appendix 3.

Table 1 illustrates how to integrate human data and non-clinical data. With regard to human data 5 different situations are presented in the left column (Y-axis), and for the non-clinical data 2, different situations (X-axis), both reflecting a type of gradient in severity of effects and risks.

In order to harmonize the labelling, it is recommended that this integration table is to be used on a regular basis for most of situations.

Although presented in discrete steps of numbers and presence of effects, the human and non-clinical data reflect a gradient in the level of concern, which cannot be expressed in discrete steps of risk. The

integration process should be applied taking into account this continuity in risk assessment. The choice of the wording belonging to the level of concern should be considered with flexibility to express factual background data.

Furthermore, the integration of the human and non-clinical data should also take into account the pharmacological properties (potential class effects) and pharmacokinetic data, as spelled out under sections 5 and 6 of this document and the therapeutic benefit of each medicinal product within all options available.

The main purpose of Table 1 is to illustrate the approach used for integration, which leads to conclusions about the risk of uncertainty (and evidence) for humans (the upper part in the boxes), and the appropriate labelling that can be used for this level of risk uncertainty/evidence.

In general, the text of the SPC section 4.6 should include clinical and non-clinical data followed by recommendations.

- With respect to clinical data section 4.6 of the SPC should:

  ➢ include comprehensive information on relevant adverse events reported in the embryo, the foetus, neonate, infant and pregnant woman, when appropriate. The frequency of such events (for example the frequency of congenital malformations) should be specified when available.

  ➢ specify the extent of the human experience if no adverse events have been reported in pregnancy (see Table 1).

- With respect to non-clinical data: only conclusions of the reproductive toxicity studies should be included in Section 4.6. Further details should be provided in Section 5.3.

- With respect to the recommendations:

  ➢ Recommendations on the use of the medicinal product during the different periods of pregnancy, including the reason(s) for these recommendations.

  ➢ Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as foetal ultrasound, specific biological or clinical surveillance of the neonate/infant).

8.1.3 Lactation

If available, clinical data from exposed breastfed infants should be mentioned as the conclusions of kinetic studies (plasma concentrations in breastfed infants, transfer of the active substance and/or its metabolite(s) into human milk…). Information on adverse reactions in breastfed infants should be included if available.

Conclusions from non-clinical studies on the transfer of the active substance and/or its metabolite(s) into milk should be given where no human data are available.

Recommendations should be given to stop or continue breast-feeding and/or to stop or continue the treatment. In cases where discontinuation of the treatment or breastfeeding is recommended, the reason(s) should be provided.

8.2 CONTRAINDICATION

A contra-indication for the whole or a defined period of pregnancy and/or a strict warning to avoid becoming pregnant must be mentioned in the label of medicinal products in situations where the medicinal product must not be administered because the risk to the pregnancy or the developing foetus/unborn child significantly outweighs the potential benefit to the mother or foetus/unborn child. This complies with the Guideline on the Summary of Product Characteristics (SPC) (See reference 3).

The most appropriate data to be used for risk assessment are those derived from human studies. Relevant human data should prevail over non-clinical information.

A contraindication in pregnancy must be included in section 4.3 (Contraindications) of the SPC. In section 4.3 a cross-reference should be made to section 4.6 (Pregnancy and lactation) of the SPC, where further information about the background to the decision should be provided.

All other clinically relevant information, including special warnings and precautions for use during pregnancy, should only be included in section 4.6. Mentioning appropriate and effective measures to prevent pregnancy in women of child-bearing potential is mandatory, where necessary.

In addition, relevant animal data should be included in section 5.3 (Pre-clinical safety data).

8.2.1 Principles for contraindication in pregnancy

A decision on whether a contraindication in pregnancy is necessary is outlined in the attached decision scheme (Appendix 2). The facts that should be taken into consideration are:

- Human experience;
- Relevant non-clinical studies;
- Need for treatment.

8.2.1.1 Human experience

In case of suspected or demonstrated malformative risk (see section 6.2.1.2 and 6.2.1.3) a contraindication should be considered.

This should certainly be the case if the new medicinal product has a chemical structure and/or pharmacological profile (mode of action) similar to that of a known human teratogen or is part of a therapeutic class known to be teratogenic in human.

8.2.1.2 Relevant non-clinical studies

In exceptional circumstances, a contraindication in humans may be based on non-clinical data only, such as:

- Pharmacology: properties known to cause direct or indirect embryo-foetal damage
- Genotoxic potential
- Embryo-foetal development: lethality, malformations, retardations, and functional changes.

Before a contraindication is established, the whole non-clinical assessment is required taking into account the severity of the signals and the exposure in relation to the human therapeutic exposure.

Section 4.6 must always cross-refer to Section 5.3 where relevant non-clinical data should be given.

8.2.1.3 Need for treatment

Where data indicate the potential for an increased risk to the developing embryo/fetus from the medicinal product, such a risk must be weighed against the potential benefit of the treatment for the pregnant woman, before a contraindication is considered.

The following points should be taken into consideration:

- Life threatening disease
- Alternative safer treatment available without compromising the therapeutic benefit.
- Treatment can be modified, deferred or avoided.

Only if either, a) there are alternative safer treatment options or, b) treatment can be delayed until the pregnancy has ended, must a contraindication in pregnancy be considered.

If there is no safer treatment option and treatment cannot be delayed then the product should not be contraindicated in pregnancy.

Clinically relevant information should be described under section 4.6 of the SPC to allow the prescriber and patient to come to an informed joint decision. This should be accompanied by any

information on how to avoid damage to the foetus/unborn child, or to reduce the probability leading to this.

8.2.2 Lactation

When a contraindication for lactation is applicable, breastfeeding can be stopped or interrupted, except in the case that lactation itself is influenced. When a contraindication is mentioned, in most cases it is because of the risk for the child. If is it possible to suspend breastfeeding during the treatment, the timing of the duration of interruption should be clearly justified.

8.3 Women of childbearing potential / Contraception

Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including pregnancy testing and contraception. Where an efficient contraception is required for patients or partners of patients during treatment, and for a defined period before starting and/or after ending treatment, the rationale should be included in the Section 4.6 of the SPC.

9 REFERENCES

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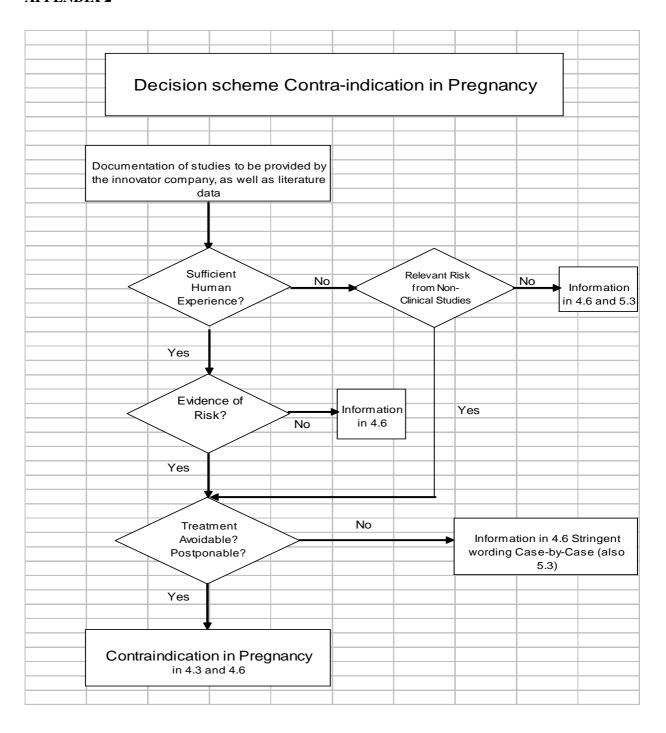
APPENDIX 1

Integration table for risk assessment and recommendation for use

TABLE 1

Human data	Non clinical data	
	Effects detected *	**No effects detected**
Human data	Conclusion from integration *Labelling* *(see appendix 3)*	Conclusion from integration *Labelling* *(see appendix 3)*
Demonstrated human teratogenicity (or fetotoxicity)	Proven risk in humans *Labelling [1]* *See also decision scheme on Contraindication*	Proven risk in humans *Labelling [1]* *See also decision scheme on Contraindication*
Supposed or suspected human teratogenicity (or fetotoxicity)	Strong suspicion of risk in humans *Labelling [2]*	Risk is possible in humans *Labelling [3]*
None or less than 300 prospective exposed pregnancies with known outcome in the 1st trimester and no increased rate of malformation identified	Risk is possible in humans, not confirmed *Labelling [4]*	Malformative risk unlikely in humans, but low evidence *Labelling [5]*
At least 300 prospective exposed pregnancies with known outcome in the 1st trimester and no increased rate of malformation identified	Malformative risk unlikely in humans. but low evidence *Labelling[6]*	Malformative risk unlikely in humans with moderate to substantial evidence *Labelling[7]*
At least 1000 prospective exposed pregnancies with known outcome in the 1st trimester and no increased rate of malformation identified	Malformative risk unlikely in humans with strong evidence *Labelling [8]*	Malformative risk unlikely in humans with strong evidence *Labelling [8]*

* Insufficient data are considered as effects detected

APPENDIX 2

Decision scheme Contra-indication in Pregnancy

Documentation of studies to be provided by the innovator company, as well as literature data

Sufficient Human Experience? — No → Relevant Risk from Non-Clinical Studies — No → Information in 4.6 and 5.3

Yes ↓

Evidence of Risk? — No → Information in 4.6

Relevant Risk from Non-Clinical Studies — Yes ↓

Yes ↓

Treatment Avoidable? Postponable? — No → Information in 4.6 Stringent wording Case-by-Case (also 5.3)

Yes ↓

Contraindication in Pregnancy in 4.3 and 4.6

APPENDIX 3

EXAMPLES OF STATEMENTS FOR USE IN SECTION 4.6 'FERTILITY, PREGNANCY AND LACTATION' OF THE SUMMARY OF PRODUCT CHARACTERISTICS

WITH RESPECT TO 'PREGNANCY'

[1] < Based on human experience *(specify)* <{Active substance} causes
congenital malformations *(specify)* when administered during pregnancy.
[or]
harmful pharmacological effects during pregnancy and/or on the foetus/new-born child.>

{Invented name} is contraindicated <during pregnancy><during {trimester} of pregnancy> *[this case is a strict contraindication]* (see section 4.3).

<Women of childbearing potential have to use effective contraception <during and up to {number} weeks after> treatment.>>

[2] < Based on human experience *(specify)* {Active substance} <is suggested / suspected to cause
congenital malformations *(specify)* when administered during pregnancy.
A <Studies in animals have shown reproductive toxicity (see section 5.3).>
[or]
B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>

{Invented name} should not be used<during pregnancy><during {trimester} of pregnancy> unless the clinical condition of the woman requires treatment with {active substance}.

<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after)> treatment. >>

[3] < Based on human experience *(specify)* {Active substance} <is suggested / suspected to cause
congenital malformations *(specify)* when administered during pregnancy.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

{Invented name} should not be used<during pregnancy><during {trimester} of pregnancy> unless the clinical condition of the woman requires treatment with {active substance}.

<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after)> treatment, >>

[4] <There are no or limited amount of data from the use of {Active substance} in pregnant women>
A <Studies in animals have shown reproductive toxicity (see section 5.3).>
[or]
B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>

{Invented name}} is not recommended < during pregnancy > <during {trimester} of pregnancy > and in women of childbearing potential not using contraception >

[5] <There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of {Active substance} in pregnant-women>
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable < to avoid the use of {invented name} <during pregnancy > <during {trimester} of pregnancy >.

[6] <A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of {Active substance}>.
A <Animal studies have shown reproductive toxicity (see section 5.3). *[or]*
B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3)>.

As a precautionary measure, it is preferable < to avoid the use of {invented name}> <during pregnancy > <during {trimester} of pregnancy >

[7] <A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity>.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of {invented name} may be considered <during pregnancy > <during {trimester} of pregnancy >, if necessary.

[8] <A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity>.

{Invented name} can be used <during pregnancy > <during {trimester} of pregnancy > if clinically needed.

[9] <No effects during pregnancy are anticipated, since systemic exposure to {Active substance} is negligible>.

{Invented name} can be used during pregnancy. *(E.g. medicinal products for which negligible systemic exposure/negligible pharmacodynamic systemic activity has been demonstrated in clinical situation)*

WITH RESPECT TO 'LACTATION'

1. < {Active substance}/metabolites are excreted in human milk and effects have been shown in breastfed newborns/infants of treated mothers. >
    [or]

    < {Active substance}/metabolites have been identified in breastfed newborns/infants of a treated mother. <The effect of {Active substance} on newborns/infants is unknown.> *[or]* <There is insufficient information on the effects of {Active substance} in newborns/infants.>
    [or]

    {Active substance}/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely.

    {Invented name}< is contraindicated during breast-feeding (see section 4.3) > *[or]* < should not be used during breast-feeding > *[or]* < Breast-feeding should be discontinued during treatment with {Invented name}> *[or]* < A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Invented name} therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.>

2. <It is unknown whether {Active substance}/metabolites are excreted in human milk>
    [or]
    < There is insufficient information on the excretion of {Active substance}/metabolites in human milk. >
    [or]
    <There is insufficient information on the excretion of {Active substance}/metabolites in animal milk>
    [or]
    <Available pharmacodynamic/toxicological data in animals have shown excretion of {Active substance}/metabolites in milk (for details see 5.3)>
    [or]
    < Physico-chemical data suggest excretion of {Active substance}/metabolites in breast milk>

    A risk to the suckling child cannot be excluded.

    Invented name} < is contraindicated during breast-feeding (see section 4.3) > *[or[* < should not be used during breast-feeding > *[or]* < Breast-feeding should be discontinued during treatment with {Invented name}> *[or]* < A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Invented name} therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

3. < No effects of {Active substance} have been shown in breastfed newborns/infants of treated mothers>
    [or]
    < No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to {Active substance} is negligible>
    [or]
    < {Active substance}/metabolites have not been identified in plasma of breastfed newborns/infants of treated mothers.>
    [or]
    < {Active substance}/metabolites are not excreted in human milk. >
    [or]
    < {Active substance}/metabolites are excreted in human milk, but at therapeutic doses of {Invented name} no effects on the breastfed newborns/infants are anticipated.>

    {Invented name} can be used during breast-feeding.