



London, 23 March 2006
EMA/CHMP/203927/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

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

DRAFT AGREED BY MULTIDISCIPLINARY EXPERT GROUP	June 2005
DRAFT AGREED BY THE SAFETY WORKING PARTY/EFFICACY WORKING PARTY/ PHARMACOVIGILANCE WORKING PARTY	November 2005
DISCUSSION AT THE HERBAL COMMITTEE FOR MEDICINAL PRODUCTS (HMPC) MEETING	March 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006

Comments should be provided to SWP Secretariat: monika.croton@emea.eu.int
Fax: + 44 20 7418 8613

KEYWORDS

Pregnancy, lactation, medicines for human use, risk assessment.

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

TABLE OF CONTENTS

1	INTRODUCTION AND BACKGROUND	3
2	PURPOSE OF THE GUIDELINE	3
3	SCOPE.....	3
4	LEGAL BASIS.....	3
5	NONCLINICAL RISK ASSESSMENT.....	3
5.1	No study.....	4
5.2	No effect	4
5.3	Effect.....	5
5.4	Class alert	6
6	CLINICAL RISK ASSESSMENT	6
6.1	Male and Female Fertility	6
6.2	Assessment of developmental effects:	7
6.3	Assessment of a malformative effect:	7
7	CONTRAINDICATION	8
7.1	Principles for contraindication in pregnancy.....	9
7.2	Human experience.....	9
7.3	Relevant non-clinical studies.....	9
7.4	Need for treatment	9
8	LABELLING:.....	10
8.1	General recommendation	10
8.2	Fertility	10
8.3	Pregnancy	10
8.4	Lactation.....	11
8.5	Women of childbearing potential / Contraception.....	11
9	REFERENCES	11
	APPENDIX 1.....	12
	APPENDIX 2.....	15

1 INTRODUCTION AND BACKGROUND

The information and advice given on how to use a medicinal product in relation to human reproduction should allow the physician to manage a number of situations. They include prescription of medicinal products to women of child bearing potential, pregnant or breast-feeding women. Information on the risks with exposure to the active substance before and during pregnancy and during lactation should thus be provided as well as recommendations on the management of risk in clinical practice. The risk assessment is based on the results of non-clinical and clinical data.

2 PURPOSE OF THE GUIDELINE

The purpose of this guideline is (1)

- to describe integration processes of non-clinical and clinical data to assess the risk of an adverse reproductive/developmental effect in human (fertility, pregnancy, health of the foetus and child) based on reproductive toxicity studies in animals and human clinical data,
- to outline how to communicate the identified risk. Information and recommendations in the Summary of Product Characteristics (SPC) on how to use the medicinal product are addressed 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, as amended. With respect to nonclinical data, the guideline refers primarily to the ICH guidelines on Reproductive Toxicity (ICH S5A, Note for Guidance on Reproductive Toxicology; Detection of toxicity to reproduction for medicinal products, CPMP/ICH/386/95; ICH S5B (M), and Note for Guidance on Reproductive Toxicology: Toxicity to Male Fertility, CPMP/ICH/136/95).

With respect to well-established and 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 *Draft* 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 clinical data should be considered in the framework of the recent Note for Guidance on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data, EMEA/CHMP/1889/04

5 NON-CLINICAL RISK ASSESSMENT

The non-clinical risk assessment should be based on the reproductive toxicity studies and all pharmacological (primary, secondary and safety) and 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 an active substance on mammalian reproduction.

Reproductive toxicity includes:

- Effects on reproduction in the parental generation (F₀ 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 (F₁ generation) prior to attainment of adult life. It includes effects induced or manifested in the embryonic or fetal period (adverse effect on the conceptus resulting from prenatal exposure, including structural or functional abnormalities) and those induced during lactation period or manifested postnatally (adverse effect on e.g. behaviour and sexual maturation).

The following points are important to take 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-fetal toxicity study. In cases where the rat or rabbit were unsuitable for testing, 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.

Whenever possible, the selected species should be responsive to the primary pharmacodynamic effect of the active substance.

- **Pharmacokinetics:**

The pharmacokinetic profile including biotransformation should be documented, to 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 passage of placenta should be available.

Information about the excretion into milk of the active substance and/or its metabolites should be available

- **Route of administration:**

It should have been the intended route for human use. Another 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 should have covered a dose resulting in minimal maternal toxicity as well as a no adverse effect dose. Dosing intervals should be close enough to reveal any dose-related trends. If excessive dose intervals have been used there is a risk of missing a 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 active substance or secondary to the poor maternal condition.

- **Toxicokinetics:**

The exposure in pregnant animals measured by plasma concentrations of the compound and/or metabolites should be assessed

- **Mechanism:**

If reproductive toxicity is identified, knowledge of the mechanism is desirable.

To allow a proper evaluation (*i.e.* assess the relevance), the available non-clinical studies must be of adequate scientific quality and conducted in accordance with Good Laboratory Practice (GLP).

5.1 No study

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 such deficiencies should be addressed in the evaluation or the lack of data should be justified.

5.2 No effect

If the animal studies do not indicate direct or indirect harmful effects in adequately designed reproductive toxicity studies, and if there is no class alert, or no effects relevant for reproductive effects identified in any pharmacological or toxicological study, this should be concluded and the evaluation process finalised.

5.3 Effect

If an effect suggesting reproductive toxicity was detected, the evaluation process should continue as outlined below in order to assess the level of concern. An effect may be 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.

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

- Data with respect to fertility

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), which may be detected in both rodents and non-rodents.

- Cross-species concordance:

The same type of reproductive toxicity is observed in more than one species. 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:

Proposal: Some general effects (e.g. growth retardation) might be sensitive to various external influences. Such reversible effects will get less weight than morphological effects especially if it is the only finding in a well-conducted study.

- Multiplicity of effects:

Multiplicity of effects refers to the observation, in a single species or animal model, of two or more effects within similar endpoints

- Adverse effects at various stages of the reproductive process:

It refers to observations, in a single species or animal model, of effects during different stages of the reproductive process.

- 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 drug-exposed animals may increase the concern for reproductive toxicity in humans. Inclusion of rare events in the SPC should be considered on a case-by-case basis. It might also lead to a signal in the risk-management plan.

Moreover, the following factors should be considered, when assessing the level of concern for the effects (s) identified.

- Maternal toxicity: The magnitude of adverse effects in the offspring versus the severity of maternal toxicity should be considered when drawing a conclusion about the relevance of the F0 toxicity to the effects observed in the offspring (F1).
- Dose response relationship: Where the intensity of any positive signal increases with the dose.
- 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, preferably in the same species. An estimation could be made by the following ratio:
 - NOAEL for reproductive toxicity / pharmacological doses or
 - 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.

The most appropriate measure of systemic exposure should be selected. Generally, it may correspond to C_{max}, AUC for the unchanged active substance and/or depending on metabolic patterns, main metabolite(s).

Species difference should be assessed. The following aspects should be considered:

- protein binding, receptor affinity, tissue distribution
- metabolic pattern. Unique metabolites in the animal do not raise concern. At the opposite, unique metabolites in human are a concern and specific studies with such metabolite could be required.

A biomarker which is relevant and possible to determine in animals and human could serve as a metric for the estimation of exposures.

- Recent historical control data from the same type of study in the laboratory in which the study was carried out.

5.4 Class alert

A class alert should be based on adverse reproductive effects previously demonstrated in humans by closely related chemical entities or an active substance with similar pharmacodynamic effects, if the pharmacodynamic effect might be related to the adverse reproductive or embryo-/fetotoxic effect (e.g. retinoids, ACE-inhibitors).

6 CLINICAL RISK ASSESSMENT

The clinical risk assessment in general will be based on various types of clinical data. These could include:

- case-reports
- case series
- epidemiological studies

This information could originate from different sources, e.g. pregnancy registries, registries of congenital malformations, teratogenic effects networks and pharmaceutical companies, and types of bibliographical data.

The assessment should take the methodology in account, 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 fetuses aborted due to malformation, etc.

Parameters such as therapeutic benefit, therapeutic alternatives, clinical practices, pharmacokinetics, extraction procedure of herbal medicinal products, etc. should be considered.

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 risk assessment should be based on these data alone.

6.1 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 that does not result in a conception for at least one year. 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 the assessment of such impairment should be undertaken. 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 Assessment of developmental effects:

The administration of a medicinal product during pregnancy may produce three major types of effects on the (unborn) child depending on the period of interfering with the developmental phase:

- A teratogenic (malformative) effect, associated with exposure at the beginning of pregnancy (the first trimester of pregnancy is the period of highest risk).
- A fetotoxic effect, which includes effects such as growth retardation or either histological or functional maturation of organs (the period of highest risk begins during the second trimester of pregnancy and continues throughout pregnancy). It needs to be considered that some effects on the offspring may not be detectable until later in life.
- A pharmacological effect in the neonate, which is mostly associated with an exposure at the end of pregnancy or during labour. The endpoint differs from the endpoint 'teratogenicity or fetotoxicity' although all endpoints could be caused by the pharmacology of the active substance.

6.3 Assessment of a malformative effect:

Structural birth defects, detected directly at birth, occur in approximately 3-5 % of all live births. Each individual type of malformations is rare; with the most common in the order of 1/1,000 live births.

Data from prospective monitoring, i.e. exposure during the first trimester of the pregnancy and with a known pregnancy outcome, may be present in different numbers of pregnancies, resulting in different levels of certainty regarding the risk with such use

- up to 300 pregnancies (no or very limited number of data),
- between 300 and 1000 pregnancies (a limited number of data)
- more than 1000 pregnancies (large number of data),
- an extensive number (not quantifiable beforehand) of data (needed to conclude on 'no risk.')

From a statistical standpoint, power-calculations indicate that with 300 pregnancies a conclusion might be reached that the drug at hand is not responsible for a more than 10-fold increase of the overall frequency of malformations. Based on around 1000 pregnancies this conclusion can be extended to not more than a 2-fold increase.

Since the frequency of malformations in the general population is relatively well known, the presence of a control group is generally not required. 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).

The number of prospectively monitored pregnancies may vary according to the frequency of lost to follow-up, spontaneous abortions and selectively interrupted pregnancy with no pathologic examination).

The relevance of the methodology of each study should be reviewed by experts before deciding whether to take the results in account.

6.3.1 A demonstrated malformative effect is defined when:

- there is clear evidence that an active substance is associated with the increase of malformations (global rate or specific malformations). This conclusion may only be drawn over time based on signals which are subsequently confirmed. The relevance has to be discussed by experts.

6.3.2 A **suggested** or **suspected** malformative risk is based on:

- several relevant case-reports involving the active substance. Causal relationship between the active substance 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 suggest 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 active substance and the malformation should be further investigated.

6.3.3 **Evidence for No indications** of an increased risk of malformations is based on reliable safety update reporting and/or (general) literature data. It results in:

- No concern arisen about any specific malformation in humans. Although this statement is unlikely to be proven statistically, the information is important for the health professional informing the patient (physician, pharmacist, midwife).
- A extensive amount of high quality, preferably prospective, data is necessary to conclude that there is 'no risk' with the use of the medicinal product in pregnancy, and thereby recommend its use, without precautionary statements in the SPC.

6.3.4 **Fetal and/or neonatal toxicity:**

A similar approach as given for the malformative risk can be used for the fetal toxicity and/or pharmacological effects in neonates if the medicinal product will be administered during the second and third trimester, or during labour.

6.3.5 **Administration during lactation**

The assessment of hazards for breastfed infants due to administration of a medicinal product to the mother during lactation relies on nonclinical, pharmacokinetic (PK) and sometimes clinical data:

- Non-clinical studies
 - Transfer into milk
 - Development of breastfed pups
 - Physicochemical and PK characteristics of the active substance, supposed to estimate absorbed quantities and their duration in milk
- Clinical data
 - Evidence of the milk transfer through analyses of human milk samples
 - Follow-up of breastfed infants of treated mothers
 - Adverse events reported in breastfed infants and related to maternal intake
 - Is the medicinal product usually administered to neonates or not?

Clinical data, when available, supersedes non-clinical data and should provide the basis of the assessment of the benefit/risk ratio of continuing treatment during breast-feeding.

Topical application on the breast should be considered according to the direct risks for the newborn.

7 **CONTRAINDICATION**

A contra-indication (of part or the complete term) in pregnancy and/or a strict warning not to become 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) (3) and corresponds to the wording "absolute contraindication" or "strict contraindication", which is used in clinical language.

A contraindication in pregnancy must be included in section 4.3 (Contraindications) of the SPC. In section 4.3 a cross-reference should be given 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, should only be included in section 4.6.

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

7.1 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.

7.2 Human experience

Experience of the use of medicinal products in human pregnancies can come from either case reports or from other more extensive studies describing the outcome of pregnancies.

Further information can be obtained if the new active substance has a chemical structure and/or pharmacological profile similar to that of a known human teratogen or is part of a therapeutic class known to be teratogenic in human.

If there are sufficient data to conclude that no evidence of risk exists this conclusion together with the data on how it was reached should be mentioned in section 4.6.

Where there is insufficient or no experience in human, the risk assessment must rely on non-clinical data.

7.3 Relevant non-clinical studies

To allow a proper evaluation, the non-clinical studies or bibliographical data must be of adequate scientific quality and preferably conducted in accordance with Good Laboratory Practice (GLP). When performing the non-clinical risk assessment for the use of a medicinal product during pregnancy, the following issues should be taken into consideration before coming to a conclusion about the relevance for the human situation and to allow a decision on a contraindication:

- Pharmacology: properties known to cause direct or indirect embryo-fetal damage
- Genotoxic potential
- Embryo-fetal development: lethality, malformations, retardations, and functional changes. Consideration of possible influences on these endpoints by maternal toxicity
- Low safety margin

Before any conclusion is made, a whole toxicological assessment is required taking into account the strength of the signals.

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

7.4 Need for treatment

In cases where data indicate that there is the potential for an enhanced risk to the developing foetus with the medicinal product, such a risk must be weighed against the potential benefit of the treatment, 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 other safer treatment options or, b) treatment can be delayed until the pregnancy has ended, must a contraindication in pregnancy be considered.

A decision for contraindication should always be based on all available data. Therefore, a proposal should only be made following discussion between non-clinical and clinical experts. 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.

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 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 fetus/unborn child, or to reduce the probability leading to this.

8 LABELLING:

8.1 General recommendation

- «Contraindication in pregnancy» should be supported by human data (teratogenicity or fetotoxicity) or by strong non-clinical data (see above and appendix 2). When a contra-indication in pregnancy or lactation is made, this should be included in Section 4.3.
- - Efforts should be made by the MAH to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential.

8.2 Fertility

- The main information on the possible effects of the medicinal product on fertility must be included in Section 4.6.
- The paragraph should include:
 - a) Clinical data if available
 - b) Relevant conclusions from non-clinical toxicity studies if available (to be discussed with toxicologists, in particular with regard to predictive value). Further details should be included in Section 5.3.
 - c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.

If appropriate, cross-references can be included in Sections 4.3, as appropriate.

- No wording on fertility is necessary if there is no human fertility data available. The lack of non-clinical data, if applicable, should be mentioned in Section 5.3

8.3 Pregnancy

With respect to non-clinical data,

- only conclusions of the reproductive studies should be included in Section 4.6. The species in which the product has been tested can be specified if they are different to the species recommended by a guideline. Further details should be provided in Section 5.3.
- the conclusions of non-clinical toxicity studies are not necessary and should not be mentioned if a product is known to be teratogenic in humans or if it is known to be non teratogenic in humans.

With respect to clinical data,

- the section 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 birth defects) may be specified when available.

- the Section should specify the extent of the human experience if no adverse events have been reported in pregnancy (e.g. very limited, limited, large experience).

Consequently, the paragraph should include:

- a) Clinical data from human experience in pregnancy with the frequency when appropriate
- b) Conclusions from developmental studies which are relevant for the assessment of the risk associated with exposure during pregnancy. Only malformative, fetotoxic and neonatal effects should be mentioned in this paragraph. Further details should be included in Section 5.3 when appropriate.
- c) Recommendations on the use of the medicinal product during the different periods of gestation. A sentence should provide the reason(s) of these recommendations.
- d) Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as fetal ultrasound, specific biological or clinical surveillance of the neonate/infant)

8.4 Lactation

If available, clinical data should be mentioned including the conclusions of the studies on the transfer of the active substance and/or its metabolite(s) into human milk (positive/negative excretion, milk:serum ratio). Further details should be included in Section 5.2. Information on adverse events in nursing neonates/infants should be included if available.

Recommendations should be given: to stop or continue breast-feeding and/or to stop or continue the treatment. In case where treatment or breastfeeding discontinuation is recommended, the reason should be provided.

Topical application on the breast should be considered according to the direct risks for the newborn.

Conclusion on animal studies on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.

8.5 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 test, contraception. Where an efficient contraception is required for patients or partners of patients during treatment and for a defined period after ending treatment, the rationale should be included in the Section 4.6 of the SPC.

9 REFERENCES

1. Concept Paper on the Development of a Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Risk Assessment of Medicinal Products on Human Reproductive and Development Toxicities: from Data to Labelling
2. Scialli, A.R. Buelke-Sam, J.L., Chambers, C.D., et al, Communicating Risks during Pregnancy: A workshop on the use of data from Animal Developmental toxicity studies in Pregnancy Labels for Drugs. Birth Defects Research (Part A) 2004, 70: 7-12.
3. Guideline on the Summary of Product Characteristics (2005). Rules governing Medicinal products in the European Community Volume 2A and 2B The Notice to Applicants.

APPENDIX 1

Annexes I and III of the Guideline on Summary of Product Characteristics were published in October 2005, but will be updated after the consultation procedure of the present document if needed. Comments on the example wording are welcomed.

STATEMENTS FOR USE IN SECTION 4.6 “PREGNANCY AND LACTATION” OF SPC

(Annex I to the “Guideline on Summary of Product Characteristics”)

[1] <{Active substance} causes birth defects (specify) when administered during pregnancy. {Invented name} is contraindicated during (trimester) 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) <with or without animal data> {Active substance} <is suspected to cause > pharmacological effects on pregnancy and/or the foetus/new-born child.>
<{Invented name} < is not recommended > <in pregnancy > <during {trimester} of pregnancy > and in women of childbearing potential not using effective contraception, unless the clinical condition of the woman requires treatment with {active substance} >

[3] <There are no or very limited amount of ^(defined in § 6.2) data from the use of {Active substance} in pregnant patients.>
<Studies in animals have shown reproductive toxicity (specify)(see section 5.3). [*or*]
<Animal studies are insufficient with respect to reproductive toxicity (specify if needed)(see section 5.3).
<{Invented name} < is not recommended > <in pregnancy > <during {trimester} of pregnancy > and in women of childbearing potential not using effective contraception >

[4] <For {Active substance}no or very limited amount of ^(defined in § 6.2) data on pregnant patients are available.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (specify) development (see 5.3).
.> As a precautionary measure, it is preferable < to avoid the use of {invented name}> <in pregnancy > <during {trimester} of pregnancy >”

[5] < A limited amount of ^(defined in § 6.2) < xxx> data on pregnant women indicate no malformative or foeto/ neonatal toxicity of {Active substance}. Animal studies have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown.
[*or*]
<Animal studies are insufficient with respect to reproductive toxicity (see 5.3)..
.> .> As a precautionary measure, it is preferable < to avoid the use of {invented name}> <in pregnancy > <during {trimester} of pregnancy >

[6] < A limited amount of ^(defined in § 6.2) < xxx >data on pregnant patients indicate no malformative or foeto/ neonatal toxicity. Animal studies do not indicate reproductive toxicity (see 5.3).
.> The available clinical data is insufficient to exclude a risk. The use of {invented name} may be considered <in pregnancy > <during {trimester} of pregnancy >, if necessary >

[7] <A fair amount of data on pregnant patients < xxx > indicate no malformative nor foeto/ neonatal toxicity.

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

[8] <A extensive amount of data on pregnant women < xxx > indicate no malformative nor foeto/neonatal toxicity.

{Invented name} can be used <in pregnancy > <during {trimester} of pregnancy >

[9] No effects on pregnancy are anticipated, since systemic exposure to (active substance) is negligible. (Invented name) can be used during pregnancy. (*E.g. topical drugs for which negligible systemic exposure has been demonstrated*)

EXAMPLE WORDINGS FOR SECTION 4.6, SUBSECTION ‘LACTATION’

(Annex III to the “Guideline on Summary of Product Characteristics”)

1. {Active substance} is not excreted in breast milk. {Invented name} can be used during lactation.
2. {Active substance} is excreted in breast milk. However, at therapeutic doses of {Invented name} no effects on the suckling child are anticipated. {Invented name} can be used during breast-feeding.
3. {Active substance} is excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of {Invented name} are administered to breast-feeding women.

Alternative recommendations (combinations of recommendations may be used):

- {Invented name} should not be used during breast-feeding
- {Invented name} is contraindicated during breast-feeding (*must also be contraindicated in 4.3*)
- Lactation should be discontinued during treatment with {Invented name}
- A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Invented name} therapy

Additional recommendation (if applicable):

Due to the long retention time of {substance} in the body, breast-feeding must not be resumed until x (days, months) after {Invented name} therapy is completed.

4. It is unknown whether {Active substance} is excreted in human breast milk. The excretion of {Active substance} in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.
5. It is unknown whether {active substance} is excreted in human breast milk. Animal studies have shown excretion of (active substance) in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.
6. It is unknown whether {Active substance} is excreted in human breast milk. Animal studies have not shown excretion of {Active substance} in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.
7. There is insufficient/limited information on the excretion of {Active substance} in human or animal breast milk. A risk to the suckling child cannot be excluded. A decision on whether to

continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.

8. There is insufficient/limited information on the excretion of (active substance) in human or animal breast milk. Physico-chemical and available pharmacodynamic/toxicological data on (active substance) point to excretion in breast milk and a risk to the suckling child cannot be excluded. {Invented name} should not be used during breast-feeding.
9. No effects on the suckling child are anticipated since the systemic exposure of the breast-feeding woman to {Active substance} is negligible. {Invented name} can be used during breast-feeding. *E.g. ear and eye drops and other topical drugs for which negligible systemic exposure has been demonstrated.*
10. No effects on the suckling child are anticipated. {Invented name} can be used during breast-feeding. *E.g. most vitamin and mineral formulations.*

APPENDIX 2

