



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Revision 1

NOTICE TO APPLICANTS

A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS October 2005

This guideline will be included in The Rules Governing Medicinal Products in the European Union
Volume 2C Notice to Applicants

MODULE 1.3 SUMMARY OF PRODUCT CHARACTERISTICS

Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004 require that in order to obtain a marketing authorisation, a Summary of Product Characteristics (SPC) in accordance with Article 11 of Directive 2001/83/EC must be included in the application¹. In accordance with Article 21 of Directive 2001/83/EC, when the marketing authorisation is issued, the Marketing Authorisation Holder shall be informed, by the competent authorities of the Member States concerned, of the SPC as approved by it. For decisions concerning centralised marketing authorisations, according to Article 10 of Regulation (EC) No 726/2004, the final Commission decision with the SPC is addressed and notified to the Marketing Authorisation Holder. Thus, the SPC forms an intrinsic and integral part of the marketing authorisation.

The SPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. As such the content cannot be changed except with the approval of the originating competent authority.

The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively. The Package Leaflet (PL) shall be drawn up in accordance with the SPC. The *Guideline on excipients in the label and Package leaflet of medicinal products for human use* is also applicable to the SPC.

It is not in the remit of the SPC to give general advice on the treatment of particular medical conditions. On the other hand specific aspects of the treatment related to use of the medicinal product or its effects should be mentioned.

This guideline provides advice on the principles of presenting information in the SPC. Applicants should maintain the integrity of each section of the document by only including information in each section, which is relevant to the section heading. However, some issues may need to be addressed in more than one section of the SPC and in such situations the individual statements may cross-refer to other sections when these contain relevant additional information.

When a guideline exists for the SPC of a specific therapeutic area (e.g. antibiotics), pharmacological group (e.g. benzodiazepines), or product type (e.g. vaccines), this guideline should be taken into account.

Separate SPCs are required for each pharmaceutical form and strength by the European Commission and certain Member States. Limited references to other strengths or pharmaceutical forms of the same medicinal product may be necessary in an SPC if the dosage regimen is based on the use of several strengths or pharmaceutical forms. For the purposes of giving information to prescribers, the SPCs of different pharmaceutical forms and strengths may be combined for appropriate products within the same range.

SUMMARY OF PRODUCT CHARACTERISTICS: NOTES ON HEADINGS

1 NAME OF THE MEDICINAL PRODUCT

(Invented) name of the medicinal product, strength, pharmaceutical form

In those sections of the SPC in which full information on the name of the medicinal product is specifically required, the name should be followed by both the strength and the pharmaceutical form. However, when otherwise referring to the medicinal product throughout the text, the strength and the pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product.

The use of pronouns (e.g. “it”) is encouraged whenever possible.

¹ Module 1.3 consists of the SPC.

Strength

The strength should be the relevant quantity for identification and use of the product and should be consistent with the quantity stated in the quantitative composition and in the posology. Different strengths of the same medicinal product should be stated in the same way, e.g. 250 mg, 500 mg, 750 mg. The use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg). However, where a range of medicinal products of the same pharmaceutical form includes strengths of more than one unit (e.g. 250 microgram, 1 mg and 6 mg), it may be more appropriate in certain cases to state the strengths in the same unit for the purpose of comparability (e.g. 0.25 mg, 1 mg and 6 mg). For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full rather than be abbreviated.

Pharmaceutical form

The pharmaceutical form should be described by the European Pharmacopoeia full standard term using plural form if appropriate (e.g. tablets). If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms. Should this not be possible, the competent authority should be asked to request a new Standard Term from the European Department for the Quality of Medicines (EDQM) of the Council of Europe. No reference should be made to the route of administration or to the container unless these elements are part of the standard term or where there are identical products, which may be distinguished only by reference to the container.

For the expression of the name and strength of (traditional) herbal medicinal products the declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product should be provided and if appropriate in section 4.3 or 4.4. A standard statement should be included at the end of the section, i.e. 'for full list of excipients, see section 6.1'. See also the *Guideline on the excipients in the label and package leaflet of medicinal products for human use* as published on the Website of the European Commission in the Notice to Applicants, Volume 3B [<http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm>].

If a diluent is part of the medicinal product, information should be included in the relevant sections (usually sections 3, 6.1, 6.5 and 6.6).

Qualitative declaration

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or the European Pharmacopoeial name if that name represents an established name in Europe. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared. References to the pharmacopoeial quality should not be included.

Where the medicinal product is a (traditional) herbal medicinal product, the qualitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

When the medicinal product is a radiopharmaceutical kit, the qualitative declaration should clearly indicate that the radioisotope is not part of the kit.

Quantitative declaration

The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per delivered dose and/or per metered dose), per unit volume, or per unit of weight and must be related to the declaration of strength in section 1.

Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) units where

appropriate) of the active entity (base, acid or anhydrous material), e.g. '60 mg toremifene (as citrate)' or toremifene citrate equivalent to 60 mg toremifene'.

Where a salt is formed *in situ* during manufacture of the finished product, the quantity of the active entity should be stated, with a reference to the *in situ* formation of the salt.

In the case of established active substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed *in situ*.

Esters and pro-drugs

If the active substance is an ester or pro-drug, the quantitative composition should be stated in terms of the quantity of the ester or pro-drug. When the active entity is an active substance of an already approved medicinal product, the quantitative composition should also be stated in terms of the quantity of this active entity.

Oral powders for solution or suspension

The quantity should be stated per unit dose if the product is a single-dose preparation or otherwise per unit dose volume after reconstitution; a reference to the molar concentration may also be appropriate in some cases.

Parenterals excluding powders for reconstitution

For single-dose parenterals, where the total contents of the container are given in a single dose ('total use'), the quantity of active substance(s) should be stated per presentation (e.g. 20 mg etc.) not including any overages or overfill. The quantity per ml and the total labelled volume should also be given.

For single-dose parenterals, where the amount to be given is calculated on the basis of the patient's weight or body surface or other variable ('partial use'), the quantity of active substance(s) should be stated per ml. The quantity per total labelled volume should also be given. Overages or overfills should not be included.

For multi-dose and large volume parenterals, the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml, etc. as appropriate, except for multidose vaccines containing 'n' doses of the same dose. In this case, the strength should be expressed per dose volume. Overages or overfills should not be included.

Where appropriate, e.g. for X-ray contrast media, and parenterals containing inorganic salts, the quantity of active substance(s) should also be indicated in millimoles. For X-ray contrast media with iodine-containing active substances, the quantity of iodine per ml should be stated in addition to the quantity of the active substance.

Powders for reconstitution prior to parenteral administration

When the product is a powder to be reconstituted prior to administration, the total quantity of active substance in the container should be stated not including overages or overfills, as well as the quantity per ml when reconstituted, unless there are several means of reconstituting, or different quantities used, which result in different final concentrations.

Concentrates

The quantity should be stated as the content per ml in the concentrate and as the total content of the active substance. The content per ml when diluted as recommended should also be included unless the concentrate is to be diluted to within a range of different final concentrations.

Transdermal patches

The following quantitative details should be given: the content of active substance(s) per patch, the mean dose delivered per unit time, and the area of the releasing surface, e.g. 'Each patch contains 750 micrograms of estradiol in a patch size of 10 cm², releasing a nominal 25 micrograms of estradiol per 24 hours'.

Multidose solid or semi-solid products

Quantity of active substance should be stated, where possible, per unit dose, otherwise per gram, per 100 g or percentage, as appropriate.

Biological products

In the case of normal immunoglobulins, the IgG subclass distribution should be stated.

In the case of vaccines, the content of active substance per dose unit (e.g. per 0.5 ml) should be stated. Adjuvants, if present, should be stated qualitatively and quantitatively.

The nature of any cellular system(s) used for production, and if relevant the use of recombinant DNA technology, including the use of the expression 'produced in XXX cells <by recombinant DNA technology>' should be mentioned in the SPC, in a pattern as set by the following examples:

- 'produced in human diploid (MRC-5) cells',
- 'produced in *Escherichia coli* cells by recombinant DNA technology',
- 'produced in chick-embryo cells' and
- 'derived from human plasma donors'.

Herbal medicinal products

The quantitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

3 PHARMACEUTICAL FORM

The pharmaceutical form should be described by the European Pharmacopoeia full standard term (see section 1). The term used in this section should be the same as the term used in section 1. However, where a European Pharmacopoeia short standard term is used on small immediate packaging material, the short term should be added in brackets in this section.

It is recommended that a visual description of the appearance of the product (colour, markings, etc.) is given, in a separate paragraph to the standard term, including information on pH and osmolarity as required e.g.

'Tablet

White, circular flat bevelled-edge tablets marked '100' on one side'

In case of tablets designed with a score line, information should be given whether or not reproducible dividing of the tablets has been shown. e.g. 'the scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses', 'the tablet can be divided into equal halves'.

In case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. Appearance of the product after reconstitution should be stated in section 4.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

Study endpoints should not normally be included unless such mention is specified as being appropriate for the indication in CHMP Notes for Guidance or Points to Consider Documents. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

Where results from subsequent studies provide further definition or information on a licensed indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.

Mandatory conditions of product usage not covered more appropriately in other parts of the SPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

When the product is indicated in a specific age group such as children/adolescents, the indication should state the age limit e.g. 'X is indicated in <children> <adolescents> from the age of X <months><years >'.

4.2 Posology and method of administration

In case of restricted medical prescription, this section should be started by specifying the conditions.

The dosage has to be clearly specified for each method/route of administration and for each indication.

Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).

Specify dose recommendations per dose interval in an appropriate way (e.g. mg, mg/kg, mg/m²) for each age category where appropriate (specify age ranges), i.e. children as specified (see also *Note for Guidance on Clinical Investigation of Medicinal Products in Children (CPMP/EWP/462/95)*, adults, and the elderly).

Short relevant instruction for correct administration/use should also be given here. In section 6.6 'Special precautions for disposal of a used medicinal product and other handling of the product' information should be placed for instructions for preparation and/or reconstitution or in section 12 and cross-referenced here.

Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the need for dose titration,
- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation,
- advice on action to be taken if one or more dose(s) is (are) missed,
- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetics) with cross-reference to section 4.4,
- the intake of the product in relation to food intake,
- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate, and
- interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SPC (e.g. 4.4, 4.5, 4.8, 5.1, 5.2).

Where relevant to the particular product, an entry such as the following should appear 'The potency of this medicinal product is expressed in <invented name> units. These units are not interchangeable with the units used to express the potency of other <active substance name> preparations'.

Additional information on special populations

Available relevant information on special populations such as renal/hepatic impairment, geriatric or paediatric patients should be presented here.

Renal/hepatic impairment

Dosage adjustments in specific patient groups should be stated e.g. regarding:

- renal insufficiency; the dose recommendation should relate as precisely as possible to the cut-off values for biochemical markers of renal impairment clinical studies and to the results of these studies.

- liver disease, specified according to the patients included in studies, for instance ‘alcohol-related cirrhosis’ and the definitions used in the studies, for instance Child-Pugh score/grade of the patients, and
- other concomitant diseases.

Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms and signs, and/or laboratory investigations, including medicinal product concentrations should be mentioned when appropriate.

Paediatric population

When the medicinal product is to be used in children, a specific sub-section ‘paediatric patients’ should be identified.

Information should be given for the different sub-populations of children i.e. according to the ICH guideline E11.

The age limits should reflect the assessment of the available documentation and relate to age intervals where a different dosing is recommended. The information given should relate to ages for which satisfactory efficacy and safety have been shown. If necessary in preterm and term newborns, information should be written taking into account the gestational age or the post-conception age.

The dose schedule studied and found satisfactory should be given in this section. Taking account of available paediatric formulations, the dose may be related to weight or body surface area depending on what has been found optimal, e.g. children age 2-4 years, 1 mg/bodyweight b.i.d. for 1 week (up to the adult dose).

If a paediatric indication has not been approved, the following text is suggested under a subheading ‘paediatric patients’:

- X is not recommended for use in children <above><below> age Y due to <a lack of ><insufficient> data on safety and/or efficacy (the age should be specified)’ (with a possible cross-reference to section 5.1 and/or 5.2)
- The experience in children is limited. There is no experience in children. See sections 4.4 and 5.2.
- ‘Use in children – there is no relevant indication for use of <Invented name> in children’ (when the indication is not relevant to this population).
- ‘X is contraindicated in children’ (cross-reference to section 4.3)

If the product has not been studied in the paediatric population or if there are insufficient data on which to base an approval for paediatric use, it should be stated that the medicinal product is not recommended in the paediatric age group until further data become available. If available, additional information on the reason for the advice, and on the use in the paediatric age groups, can be included in sections 4.4, 5.1 or 5.3, as appropriate, together with a cross reference from this section.

Any such statement(s) regarding paediatric age groups should be transparent and reflect the available data.

In exceptional cases where the “adult formulation” of a medicinal product includes an indication and a posology for use in children, or includes, at least, posology recommendations for use in children, and where no adequate paediatric formulation can be developed based on duly justified scientific grounds (i.e. where the extemporaneous preparation of a formulation for paediatric use from the adult one is necessary), relevant instructions for the extemporaneous preparation shall be included in section 6.6 with a cross-reference in section 4.2. Such information shall be provided by the Marketing Authorisation Holder with a view to improve the quality, safety and efficacy of such extemporaneous preparations for use in children.

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include particular clinical diagnosis, concomitant

diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines). The situations must be unambiguously, comprehensively and clearly outlined.

Other medicines or classes of medicine, which must not be used concomitantly or consecutively should be stated, either based on data or strong theoretical reasons. If applicable a cross-reference to section 4.5 should be given.

In general, patient populations not studied in the clinical trial programme should be mentioned in section 4.4 and not in this section unless a safety issue can be predicted (e.g. use of renally cleared substances with narrow therapeutic margin in renal failure patients). If, however, patients have been excluded from studies as being contraindicated on serious grounds of safety, they should be mentioned in this section. If applicable a cross-reference to section 4.5 should be given.

Only if pregnancy is strictly contraindicated, should it be mentioned here. In section 4.6, a cross-reference should be given and further information about the background be provided.

Hypersensitivity to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients (see *Guideline on excipients in the label and package leaflet of medicinal products for Human Use*).

For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable.

4.4 Special warnings and precautions for use

The order of warnings and precautions should be determined by the importance of the safety information provided.

The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product. Patient groups in which use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not to be repeated here. The below mentioned particulars should be described:

- The conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled.
- Special patient groups, such as elderly and children, that are likely to experience product or class related adverse reactions (ADRs) occurring under normal conditions of use e.g. specified age groups, patients with renal, hepatic impairment (including the degree of impairment, such as mild, moderate or severe) or cardiac failure (including the NYHA classification).
- Circumstances where all patients are at risk of a specified adverse reaction, but the incidence or severity of the reaction differs in particular populations.
- Serious adverse reactions to which the prescriber needs to be alert, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.
- When the outcome of an adverse reaction is particularly serious and/or frequent, this could be emphasised by presenting the statement at the top of this section.
- If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.
- Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious ADR, a statement should be included. Any need for specific clinical or laboratory monitoring should be stated. If dose reduction is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

- Clinically relevant interactions where in general the use of the combination should be avoided should be mentioned here with a cross-reference to section 4.5.
- Any warnings necessary for excipients or residues from the manufacturing process.

In exceptional cases, especially important safety information may be included in bold type within a box.

Any adverse reactions described in this section or known to result from conditions mentioned here must also be included in section 4.8.

In case of immunologicals, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient.

Specific interaction with biological test should be mentioned when appropriate, e.g. Coombs test and Beta-lactams.

Descriptions of warnings and precautions regarding pregnancy and lactation, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and 4.5, respectively.

4.5 Interaction with other medicinal products and other forms of interaction

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and *in vivo* pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product. This includes *in vivo* interaction results which are important for extrapolating an effect on a marker ('probe') substance to other medicinal products having the same pharmacokinetic property as the marker.'

Interactions affecting the use of this medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others.

Interactions referred to in other sections of the SPC should be described here and cross-referenced from other sections.

The order of presentation should be contraindicated combinations, those where concomitant use is not recommended, followed by others.

The following information should be given for each clinically relevant interaction:

- a. Recommendations: these might be
 - contraindications of concomitant use (cross-refer to section 4.3),
 - concomitant use not recommended (cross-refer to section 4.4), and
 - precautions including dose adjustment (cross-refer to sections 4.2 and 4.4), mentioning specific situations where these may be required; for the actual dose recommendation, cross-refer to section 4.2.
- b. Any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters.
- c. Mechanism, if known.

Interactions not studied *in vivo* but predicted from *in vitro* studies or deducible from other situations or studies should be described if they result in a change in the use of the medicinal product, cross-referring to sections 4.2 or 4.4.

This section should mention the duration of interaction when a medicinal product with clinically important interaction (e.g., enzyme inhibitor or inducer) is discontinued. Adjustment of dosing may be required as a result. The implication for the need for a washout period when using medicines consecutively should also be mentioned.

Information on other relevant interactions such as with herbal medicinal products, food or, pharmacologically active substances not used for medical purpose, should also be given. With regard

to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated.

Results demonstrating an absence of interaction should only be mentioned here if this is of likely major interest to the prescriber.

If no interaction studies have been performed, this should be clearly stated.

Additional information on special populations

If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g., patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly etc, this information should be given here. If the medicinal product is indicated in children and interaction studies have been performed in adults only, this information should be given together with recommendations on concomitant use.

Paediatric population

Information specific to a special age group should be given here.

If interactions exist that are specific to children this information could be given under a subheading 'paediatric patients'. General effects of a drug on enzymes are probably the same in adults and children. However, the resulting exposure and clinical consequences of a pharmacokinetic interaction can differ between adults and children, Therefore, if the interaction studies have been performed in adults, the statement 'Interaction studies have only been performed in adults' should be included if considered relevant to the prescriber. This is especially important if any specific dose recommendations are made. The same also applies to pharmacodynamic drug interactions.

In cases where there is an interaction with food leading to a recommendation on co-administration with a meal or specific food, it should, if possible, be noted whether this information is relevant for children (especially newborns and infants) whose diet may be totally different (100 % milk in newborns versus maybe 0 % in adults) compared to the study setting leading to the recommendation.

If no interaction studies have been performed, this should be clearly stated.

4.6 Pregnancy and lactation

General recommendation

'Contra-indication in pregnancy' should be supported by human data (teratogenicity or fetotoxicity) or by strong nonclinical data. When a contra-indication in pregnancy or lactation is made, this should be included in section 4.3.

Efforts should be made by the Marketing Authorisation Holder to provide the reasons for recommendations for use in pregnant or lactating women, and in women of childbearing potential.

The following should be mentioned:

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 effective 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 this section (see Annex 1).

Pregnancy

With respect to nonclinical data,

- only conclusions of the reproductive studies should be included in this section. 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 nonclinical 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 safe in humans.

With respect to clinical data,

- the section should include comprehensive information on relevant adverse events reported in the embryo, the fetus, neonates and pregnant women, 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 (no experience, limited 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).

Cross-references can be included in sections 4.3, 4.4 and 4.8, as appropriate.

Examples of the wording of this section are given in Annex 1.

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 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.

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.

Example wordings to be used in this section are appended in Annex 3.

Fertility

No wording on fertility is necessary if there is no (human or nonclinical) fertility data available.

The main information on the possible effects of the medicinal product on male and female fertility must be included in section here.

The paragraph should include:

- a) Clinical data if available.
- b) Relevant conclusions from nonclinical 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 necessary, cross-references can be included in section 4.3, as appropriate.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile, reported Adverse Reactions and/or specific studies on a relevant target population addressing the performance related to driving or using machines, specify whether the medicinal product has a) no or negligible influence b) minor or moderate influence or c) major influence on these abilities. Effects of the disease itself on these abilities should not be discussed.

For situations b and c, special warnings/precautions for use should be mentioned.

4.8 Undesirable effects

This section should provide comprehensive information based on all adverse reactions (ADRs) from clinical trials, post-marketing studies or spontaneous reports attributed to the medicinal product with at least reasonable suspicion and on a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. In this context, all adverse reactions should be included in the SPC if they are at least possibly causally related, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC.

It is important that the whole section should be worded in concise and specific language and it should not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability. Statements on lack of proof of causal association are not helpful and should not be included.

In order to provide clear and readily accessed information, it should be structured according to the following recommendations:

- a. A general description will be necessary for most products. It should state what are the most serious and/or most frequently occurring ADRs. It should be placed before the detailed and specific information presented in the table(s) (see below b.). This description, which should be as brief as possible, should start by providing an estimate of the overall percentage of treated patients expected to experience adverse reactions. This information must be consistent with the figures presented and must not contain general statements such as ‘well tolerated’, ‘ADRs are normally rare’ etc. Examples of acceptable statements (addressing overall and organ specific frequency related to the target population) are given below:

‘Approximately 15% of patients can be expected to experience adverse reactions. These are mainly dose dependent and due to the pharmacologic effects of the medicinal product.’
or

‘ADR are rare (<1/1,000). At the beginning of therapy, epigastric pain, nausea, diarrhoea, headache or vertigo may occur: these reactions are usually mild and disappear within a few days even if treatment is continued (see also section (c) below).’

‘The most commonly reported ADRs are dizziness and headache, both occurring in approximately 6% of patients.’

‘About 30% of treated patients experience adverse reactions: they usually occur within the first three months after the start of therapy. Dose-related ADR, such as gastrointestinal reactions and headache, can sometimes be alleviated by reducing the dose (see also section (c) below.’

- b. A single table of adverse reactions according to the MedDRA system organ class. The system organ classes should be presented in the order shown in Annex 2. Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any ADR should be assigned to the most relevant SOC related to the target organ. For example, ‘Liver function test abnormal’ should be assigned to

the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'. Within each system organ class, the ADRs should be ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

The names used to describe each of the frequency groupings should follow standard terms established in each official language. Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness.

The expressions isolated/single cases/reports should not be used. If for a specific ADR a frequency cannot be estimated or a frequency category not be chosen an additional category frequency 'not known' may be added.

The choice of the frequency category to which any ADR will be assigned is based on frequency data derived from a study (clinical trial or epidemiological study) designed in such a way that when a specific adverse event had been reported in a patient it would have been detected within the defined observation period, reported, and assessed at least as a 'possible' reaction. This generally requires the use of adequate data collection and causality evaluation methods. In this situation, it is possible to calculate a point estimate of the crude incidence rate and its confidence interval, using standard statistical methods and taking into account the nature of the data (numerator, denominator, time dimension). The point estimate should be used to allocate an ADR to a frequency category.

If the choice of the frequency category is based on more than one suitable study the category representing the highest frequency should be chosen unless application of a more specific method for detection of the ADR has been applied and thus resulted in an estimate of clearly higher validity, e.g. an integrated analysis across the suitable studies. The category to be chosen for each ADR should not be representing differences (calculated against placebo or other comparator) but crude incidence rates.

The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category in any situation. If it is decided that an ADR detected by spontaneous reports should be included, each adequately designed study where this ADR could have been detected should be reviewed. If no valid estimate of the incidence rate can be derived from these studies it has to be classified as 'Not known'. When various galenical/pharmaceutical formulations of a medicinal product are available, appropriate clinical trial data for suitable formulations may be combined for the assessment of frequency categories (e.g. various oral or enteral formulations). This would aim to obtaining more robust results. In the case of different modes of application (e.g. enteral versus parenteral versus inhalation etc.), these should be dealt with separately.

A tabulation of ADR frequency estimates from clinical trials, stated as a fraction expressed per 1,000 exposed patients (incidence rates, related confidence intervals), which do not serve the purpose of assignment to the defined frequency categories may only be included when it is of particular relevance to the patient and/or prescriber to be informed of certain risks and related frequency estimates. In these cases it is preferable that the data should be based on pooled study results or large targeted studies performed under actual market conditions.

When data come from a placebo-controlled trial or a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline incidence rate, and if the ADR is considered important, the background incidence may be provided in a footnote, or results may be presented as an added column or in a separate table.

In these exceptional instances where more precise frequencies are stated, the figures should be annotated with a footnote describing how the data were obtained. The methods used to derive the figures will vary but must be appropriate to the circumstances. The annotation might read, for example:

'Excess incidence compared with placebo in pooled data from clinical trials involving x patients taking the medicinal product and y patients taking placebo, where the placebo incidence was z',

'Incidence of the suspected adverse reaction in an observational post study in x patients'.

If there are only a few adverse reactions in total in this section, tabulation by system organ class may be unnecessary.

Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and 'see section c)' should be included as a footnote.

- c. This section should include information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information may describe for example reversibility or time of onset the severity, duration of reaction, mechanism of the reaction (if of clinical relevance), or dose relationship. Mention should be made here of any differences between different dosage forms in respect of adverse reactions. In the case of combination products, a statement should be included in this section pointing out which particular adverse reactions are usually attributable to which component of the combination, where known.

Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur (if of particular importance) should be mentioned under section 4.4 and cross-referenced here.

Any adverse reactions resulting directly from an interaction should be mentioned here and cross-referenced to section 4.5.

- d. This section should include adverse reactions, which apply to the therapeutic chemical or pharmacological class-adverse reactions of very low frequency or with delayed onset of symptoms which may not have been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class. The fact that this is a class attribution should be mentioned.

Any undesirable event warnings necessary for excipients or residues from the manufacturing process should be included.

Additional information on special populations

Information specifically observed in other special populations such as elderly patients, patients with renal insufficiency, patients with hepatic insufficiencies, other concomitant diseases etc.

Paediatric population

If some undesirable effects are specifically observed in children or if altered frequencies of undesirable effects are observed, this information should be given in a subsection entitled 'paediatric patients'. If possible, the information could be divided into ICH E11 age groups. If a similar safety profile is expected in children as in adults this could be stated. For existing products it is possible that the requirements cannot be fulfilled because the necessary information is not available. In other cases, the recommendations apply.

4.9 Overdose

Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on accidental mistakes and suicide attempts by patients.

Describe management of overdose in man, e.g. in relation to specific agonists/antagonists or methods to increase elimination of the medicinal product e.g. dialysis.

Additional information on special populations

Information specifically observed in other special populations such as elderly patients, patients with renal insufficiency, patients with hepatic insufficiencies, other concomitant diseases etc.

Paediatric population

If there are specific paediatric considerations, there should be a sub-section entitled ‘paediatric patients’.

It might be useful to have a special mentioning for those medicinal products which can cause a fatal poisoning in the special risk group of young children (for instance a bodyweight of 10 kg could be used as the limit) if just a single tablet is ingested. This is a limited special group of medicines, which should be kept with extra care.

5. PHARMACOLOGICAL PROPERTIES

Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and to other health-care professionals*, taking into account the approved therapeutic indication(s) and the potential adverse drug reactions. Statements should be brief and precise.

5.1 Pharmacodynamic properties

Describe:

- Pharmacotherapeutic group (ATC code). If an ATC code is not yet available, this should be mentioned as ‘not yet assigned’.
- Mechanism of action (if known)
- Pharmacodynamic effects.
- Clinical efficacy and safety

It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced and summarise evidence from relevant studies supporting the indication.

If information from subgroup or post hoc analyses that is considered clinically relevant is presented and identified as such, this should be in a balanced way, which reflects the limited robustness of both positive and negative secondary observations. The magnitude of effects should be described using relative and absolute figures.

[For products approved under ‘conditional approval’ in the centralised procedure, include the following statement:]

<This medicinal product has been authorised under a so-called ‘conditional approval’ scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency (EMA) will review new information on the product every year and this SPC will be updated as necessary.>

[For products approved under ‘exceptional circumstances’, include the following statement:]

<This medicinal product has been authorised under ‘Exceptional Circumstances’.

This means that <due to the rarity of the disease> <for scientific reasons> <for ethical reasons> it has not been possible to obtain complete information on this medicinal product.

The {name of Agency} will review any new information which may become available every year and this SPC will be updated as necessary.>

5.2 Pharmacokinetic properties

Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.

Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.

Pharmacokinetics items, which could be included in this section when relevant, are given below.

- a. General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility etc.
- b. General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.
 - **Absorption:** complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; T_{max}; the influence of food; in case of locally applied medicinal product the systemic bioavailability.
 - **Distribution:** plasma protein binding; volume of distribution; tissue and/or plasma concentrations; pronounced multi-compartment behaviour.
 - **Biotransformation:** degree of metabolism; which metabolites; activity of metabolites; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.
 - **Elimination:** elimination half-lives, the total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites.
 - **Linearity/non-linearity:** linearity/non-linearity of the pharmacokinetics of the new compound with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.

Additional relevant information should be included here.

- c. Characteristics in patients
 - Variations with respect to factors such as age, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic insufficiency, including degree of impairment. If this influence on the pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-referral to 4.2 when applicable).
- d. Pharmacokinetic/pharmacodynamic relationship(s)
 - Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or a side effect).
 - Contribution (if any) of metabolite(s) to the effect.

5.3 Preclinical safety data

Information should be given on any findings in the preclinical testing which could be of relevance for the prescriber, in recognising the safety profile of the medicinal product used for the authorised indication(s), and which is not already included in other relevant sections of the SPC.

During the development of a new medicinal product, a variety of preclinical studies will be performed. These are assessed by the competent authority when evaluating the application. If the results of the studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SPC.

The findings of the non-clinical testing should be described in brief and qualitative statements as outlined in the following example statements:

- Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

- Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
- Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

Conclusions on the environmental risk assessment on the product should be included where relevant, with reference to section 6.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks. Further details on the excipients to be declared may be found in the section on definitions and examples in the *Guideline on the Excipients in the Label and Package Leaflet of Medicinal Products for Human Use*. For transdermal patches, all ingredients of the patch (including the adhesive, release liner and backing film) should be mentioned.

The active substance itself, residues of substances used during manufacture of the finished product (for example, solvents, head-space gases or antibiotics in vaccine manufacture), lubricants for pre-filled syringes and constituents of capsule shells for inhalation powders not intended to be taken should not be included.

However, certain residues such as residues of antibiotic or other antimicrobial agents used in production that are known allergens with a potential for inducing undesirable effects should be mentioned in section 4.3.

Excipients should be referred to by their recommended INN if existing, accompanied by the salt or hydrate form if relevant or by their European Pharmacopoeia name. If an excipient has neither an INN nor European Pharmacopoeia name, it should be described by its usual common name. References to the pharmacopoeial quality should not be included. E numbers should be given where they exist and when the excipient is listed in the *Guideline on the excipients in the label and package leaflet of medicinal products for human use* (as having recognised action or effect), along with the common name of the excipient.

The ingredients in excipient mixtures should be listed individually. In cases where the full composition of a flavour or fragrance is not known to the applicant, they may be declared in general terms (e.g. 'orange flavour', 'citrus perfume'). However, any of the components, which are known, or which have a recognised action or effect must be included.

Ingredients that may or may not be added for the pH adjustment should be followed by the parenthesis '(for pH-adjustment)'

Invented names or general descriptive names such as 'printing ink' should not be used in place of the common name of an ingredient or of a mixture of ingredients but may be used in conjunction with the name(s) of the ingredient(s), so long as it is clear which ingredients are described by the name.

Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipients, e.g. 'pregelatinised starch'.

For clarity, it is recommended that each excipient be listed on a separate line. It can be useful to list excipients according to the different parts of the product, e.g. tablet core/coat, capsule contents/shells, etc. For products that are presented in more than one container or in dual-chamber containers, the excipients should be listed per container or per chamber.

Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations are designated in section 6.1.

6.2 Incompatibilities

Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated. This is particularly important for medicinal products to be reconstituted and/or diluted before parenteral administration. Significant interaction problems, e.g. sorption of products or product components to syringes, large volume parenteral containers, tubing, administration sets, etc. should be stated.

Statements concerning compatibility of the product with other medicinal products or devices should not be included in this section but in section 6.6. Statements concerning pharmacological incompatibilities with food should be included in section 4.5. If appropriate, the standard statement, 'Not applicable', should be included.

For certain pharmaceutical forms, e.g. parenterals, either of the following standard statements should be included as appropriate:

- *'In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.'*
- *'This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.'*

6.3 Shelf life

The shelf life should be given for the medicinal product as packaged for sale and after dilution or reconstitution or after first opening if appropriate.

A clear statement of the shelf life should be given, in an appropriate unit of time.

For statements to be included regarding in-use shelf lives of sterile products, consult the *Note for Guidance on maximum shelf life for sterile products for human use after first opening or following reconstitution*. An in-use shelf life may need to be stated for other medicinal products if development studies have found it to be necessary.

No reference should be made to the container unless there are different shelf lives for different containers. Storage conditions should not be included, except for the storage conditions after opening (see the corresponding guideline). Statements such as 'Do not use after the expiry date' should not be included.

6.4 Special precautions for storage

Storage warnings should use one or more of the standard statements from the *Note for Guidance on declaration of storage conditions in the product information of medicinal products*.

For storage of sterile products that have been opened, diluted or reconstituted, a cross-reference should be made to section 6.3.

In exceptional circumstances information may be given on storage under conditions other than those stated in the label and leaflet and on the approved short-term shelf life applicable under these conditions.

Note that if a specific storage warning is required, the warning should be consistent between the SPC, label and PL.

A warning to keep the product out of the reach and sight of children should not be included.

6.5 Nature and contents of container

Reference should be made to the immediate container using the European Pharmacopoeia standard term; the material of construction of the immediate container should be stated ('Type I glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, inhaler devices, desiccant. The container of any solvent provided with the medicinal product should also be described. Excessive detail, e.g., concerning the colour of the stopper, the nature of the heat-seal lacquer, should usually not be included. Examples on the text in this section:

'<Volume> ml suspension in a pre-filled syringe (type I glass) with plunger stopper (chlorobutyl rubber) with or without needle in pack sizes of 5 or 10.'

'HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack-sizes of 30, 60 or 90 film-coated tablets.'

All pack sizes should be listed. Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If appropriate, a standard statement, 'Not all pack sizes may be marketed', should be included, in order to alert health professionals to the fact that not all listed pack sizes may be available for prescribing or dispensing.

Multiple unit packs for distribution purposes only do not constitute new pack sizes for marketing of the product and should therefore not be included in this section.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product²

Instructions for disposal should be included here, if appropriate for the product.

Where special precautions for the disposal of certain products such as cytotoxics and some biological products or waste material derived from it are advised, e.g. in the case of products containing live organisms, these should be stated in this section, as should, where relevant, the disposal of items which come into contact with the product, such as spoons used to administer oral vaccines.

If applicable, e.g. for cytotoxics, the following standard statement should be included, 'Any unused product or waste material should be disposed of in accordance with local requirements.'

If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the standard statement, 'No special requirements.' should be included.

Any directions necessary for the accurate preparation of certain products such as cytotoxics and some biological products and/or necessary for the protection of persons preparing or handling the product should be stated.

In section 4.2, instructions on handling of the product by the doctor, other health personnel, or patient should be included, as well as general information concerning the administration of the product (whether administered by the patient or the health personnel). If instructions for use/handling are needed where the medicinal product has to be prepared before use, e.g. where it must be suspended or diluted, this information has to be given here.

For clarity, a cross-reference in section 4.2 to the relevant information in section 6.6 could be included, e.g. 'For instructions on dilution of the product before administration, see section 6.6.'

It is recommended that only information necessary for the pharmacist or other health personnel to prepare the product for administration to the patient should be included here.

Information on the preparation (e.g. the suspension of a powder for injection, or preparing a dilution) of the medicinal should be included in section 6.6, regardless of who prepares the product (e.g. pharmacist, doctor, other health personnel, patient). In the case of products for reconstitution, the appearance of the product after reconstitution should be stated.

Statements concerning compatibility of the product with other medicinal products or devices can be given here provided the data have been provided in the dossier.

Detailed instructions for the preparation and quality control of the extemporaneous formulation from the appropriate "adult" dosage form and additional information on extemporaneous formulations for use in children shall be provided and, where appropriate, the maximum storage time during which such preparation will conform to its specifications.

² This section is reflected in the QRD template in the section 6.6 'Special precautions for disposal'

7 MARKETING AUTHORISATION HOLDER

Name and permanent address or registered place of business of the Marketing Authorisation Holder. Telephone, fax numbers or e-mail addresses may be included (no websites or emails linking to websites).

8 MARKETING AUTHORISATION NUMBER(S)

Item to be completed by the competent authority or by the Marketing Authorisation Holder once the Marketing Authorisation has been granted. For medicinal products for which the European Commission is the Competent Authority, the number to be included in this section is the number in the Community Register.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Item to be completed by the competent authority or by the Marketing Authorisation Holder once the Marketing Authorisation has been granted or renewed. Both the date of first authorisation and, if the authorisation has been renewed, the date of the (last) renewal should be stated in the format given in the following example:

Date of first authorisation: 3 April 1985

Date of last renewal: 3 April 2000

10 DATE OF REVISION OF THE TEXT

Leave blank in case of a first Marketing Authorisation.

For medicinal products for which the European Commission is the Competent Authority: date of approval of latest variation or transfer, e.g. the latest Commission Decision amending the SPC, implementation date of the Urgent Safety Restriction or date of (EMEA) notification amending the annexes to the Marketing Authorisation.

For products for which Member States are the Competent Authorities: date of approval of latest variation or implementation date of the Urgent Safety Restriction resulting in a revision of the SPC.

Item to be completed by the competent authority or by the Marketing Authorisation Holder at time of printing the SPC.

11 DOSIMETRY (IF APPLICABLE)

Full details of internal radiation dosimetry should be included in this section for radiopharmaceuticals. For all other products, this section should be excluded.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform to its specifications.

Special instructions relating to the disposal of containers and unused contents should also be included.

ANNEX 1

This annex is currently under review. In the meantime, the below-mentioned statements still apply.

1. {Generic name} causes/is suspected to cause serious birth defects when administered during pregnancy.
{Trade name} is contraindicated (only in case of a strict contraindication see section 4.3) in pregnancy.
and if necessary
Women of childbearing potential have to use effective contraception during (and up to x weeks after) treatment.
2. {Generic name} has harmful pharmacological effects on pregnancy and/or the foetus/newborn child.
{Trade name} should not be used during pregnancy unless clearly necessary (these circumstances should be specified).
3. There are no adequate data from the use of {Generic name} in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
or
Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development (see section 5.3). The potential risk for humans is unknown.
{Trade name} should not be used during pregnancy unless clearly necessary (these circumstances should be specified where possible).
4. For {Generic name} no clinical data on exposed pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing to pregnant women.
5. Data on a limited number (.....) of exposed pregnancies indicate no adverse effects of {Generic name} on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
or
Animal studies are insufficient with respect to effects on pregnancy/ and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development (see section 5.3). The potential risk for humans is unknown.
Caution should be exercised when prescribing to pregnant women.
6. Data on a limited number (.....) of exposed pregnancies indicate no adverse effects of {Generic name} on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing to pregnant women.
7. Data on a large number (.....) of exposed pregnancies indicate no adverse effects of {Generic name} on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available.
Caution should be exercised when prescribing to pregnant women.

8. Well-conducted epidemiological studies indicate no adverse effects of {Generic name} on pregnancy or on the health of the foetus/newborn child.
{Trade name} can be used during pregnancy.
9. In case of interaction with oral contraceptives information should also be given in section 4.5.
{Generic name} adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during (and up to x weeks after) treatment.
or
The concomitant medication [Generic name] adversely interacts with oral contraceptives (OCs). Therefore an alternative, effective and safe method of contraception should be used during (and up to x weeks after) treatment.
10. In case of male-mediated effects on pregnancy outcome information should also be given in section 4.4.
Both sexually active men and women should use effective methods of contraception during (and up to x weeks after) treatment

ANNEX 2

THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES TERMINOLOGY (MedDRA)

All ADRs should be grouped according to the MedDRA system organ classes (SOC). As a general rule, MedDRA terms should be classified according to the most relevant SOC related to the target organ.

A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader. For example, it may be helpful on some occasions – solely in the context of the SPC - to use secondary SOC locations of some MedDRA Preferred Terms (PT), or sometimes to use locations that do not strictly accord with the MedDRA architecture. For example, if the terms ‘Liver function test abnormal’, ‘Hepatitis’ and ‘Hepatic encephalopathy’ are to be included in an SPC, it would be acceptable to include them all under the ‘Hepato-biliary SOC’ instead of distributing the reactions among the ‘Hepato-biliary disorders’, ‘Nervous system disorders’ and ‘Investigations System Organ Classes’ as dictated by their primary location in MedDRA.

SOC LIST - INTERNATIONALLY AGREED ORDER

- Infections and infestations
- Neoplasms benign and malignant (including cysts and polyps)
- Blood and the lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Nervous system disorders
- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders
- Hepato-biliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal, connective tissue and bone disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital and familial/genetic disorders
- General disorders and administration site conditions
- Investigations
- Injury and poisoning
- Surgical and medical procedures
- Social circumstances

ADR descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the PT level, although there may be instances where the use of Lowest Level Terms (LLT) or group terms, such as high-level terms (HLT) may be appropriate. It is acceptable to adapt the names of the MedDRA group terms if this makes their meaning more transparent to the reader of the SPC; e.g. the HLT *Genitourinary tract disorders NEC*, if otherwise appropriate for the SPC under consideration, could be presented without the suffix ‘NEC’. The use of the suffixes NEC and NOS are not appropriate for inclusion in the SPC. The adverse reaction term should be expressed in natural word order, e.g. ‘Interstitial pneumonia’ in preference to ‘Pneumonia interstitial’. It may be appropriate to modify MedDRA terms in other ways in the interests of comprehensibility. The most widely recognised term for a particular condition should be used, e.g. the

LLT 'Churg Strauss syndrome' might be more appropriate than the PT 'Allergic granulomatous angiitis'.

Within each MedDRA SOC, ADRs should be classified according to their frequency of occurrence. Prior to estimating frequency of occurrence of adverse events from systematic studies (clinical trials or other sources), appropriate levels of the MedDRA hierarchy should be used in order to group together clinically related conditions in a meaningful way. For example, if 'postural dizziness', 'exertional dizziness' and 'unspecified dizziness' were each reported by 2% of patients, this might reasonably be represented in the SPC as 'Dizziness' occurring in 6% of patients (assuming that only one report of dizziness applied to each patient). It may also be appropriate to use *ad hoc* groupings of terms, or to adapt MedDRA group terms if the established MedDRA group terms are not completely suitable, e.g. reports of adverse reactions represented as the MedDRA PT 'Diarrhoea', 'Diarrhoea aggravated', 'Loose stools', 'Stools watery', and 'Intestinal hypermotility' are present in MedDRA under 3 separate HLT – 'Diarrhoea (excl infective)', 'Gastrointestinal spastic and hypermotility disorders' and 'Faeces abnormal'. These HLTs may not be useful for representing the findings in the SPC. In the interests of making the SPC relevant and comprehensible to clinicians, these might all reasonably be represented as the single term 'Diarrhoea', and the total number of cases with the respective MedDRA PT counted together in order to estimate frequency of occurrence.

ANNEX 3

EXAMPLE WORDINGS FOR SECTION 4.6, SUBSECTION 'LACTATION'

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.*