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ENTERPRISE DIRECTORATE-GENERAL

Pharmaceuticals and cosmetics

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NOTICE TO APPLICANTS

A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS

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This guideline will be included in The Rules governing Medicinal products in the European Community Volume 2A and 2B The Notice to Applicants

PART I B 1 SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Article 4a of Directive 65/65/EEC, as amended, a proposal for a summary of product characteristics (SPC) must be included in the application. Part I B consists of the proposal for the SPC. Further, Article 4b of Directive 65/65/EEC require that the content must be approved by the competent authority. 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. It is the definitive statement between the competent authority and the marketing authorisation holder and it is the common basis of communication between the competent authorities of all the Member States. 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 content of the package leaflet must be consistent with the SPC but in a wording that can be easily understood by non-professionals.

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.

The competent authorities have previously agreed to accept the sequence given below for the presentation of information in the SPC. 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 (e.g. contra-indications plus interactions). 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) or pharmacological group (e.g. benzodiazepines), this guideline should be taken into account.

For radiopharmaceuticals, a specific annex will be prepared.

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 advertising or 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

(Trade) name of 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, even if there is only one strength and/or pharmaceutical form. However when otherwise referring to the medicinal product throughout the text, strength and 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 is encouraged where it improves the readability of the text.

Strength

The strength should be the relevant quantity for the 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, for example, 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 purposes of comparability (e.g. 0.25 mg, 1 mg and 6 mg). Micrograms should be always spelled out in full rather than abbreviated, for safety reasons.

Pharmaceutical form

The pharmaceutical form should be described by the European Pharmacopoeia full standard term. 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.

It must be noted that there are some situations where the expression of the strength or pharmaceutical form is not straightforward, e.g. radiopharmaceuticals diagnostic test kits, vaccines and other biological, biotechnological medicinal products. In such cases, it may be acceptable not to include the strength and/or the pharmaceutical form.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) should be provided. Excipients should not be mentioned, however a standard statement should be included at the end of the section, 'For excipients, see 6.1'.

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. 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 of how and from what they were prepared. References to the pharmacopoeial quality should not be included.

Where the medicinal product is a 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 puff), per unit volume, or per unit of weight.

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)'.

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 and in terms of the quantity of the active entity if that entity is the active substance of an already approved medicinal product.

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

For single-dose parenterals, the quantity of active substance(s) should be stated per ml and per total labelled volume.

For multi-dose and large volume parenterals or parenterals where the dose is given on a ml/kg basis, the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml, etc. as appropriate.

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, 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 (for example, per 0.5 ml) should be stated. Adjuvants, if present, should be stated qualitatively and quantitatively.

Where relevant, the nature of any cellular system used to manufacture the medicinal product (e.g. human plasma donors, MRC-5 human diploid cells, Escherichia coli) should be stated briefly.

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 of this guideline). The term used in this section should be the same as the term used in section 1.

It is recommended that a visual description of the appearance of the product (colour, markings, etc.) is given, in a separate paragraph or line to the standard term, e.g.

‘Tablet.

White, circular flat bevelled-edge tablets marked ‘100’ on one side.’

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should define the target disease distinguishing between treatment, primary prevention, secondary prevention and diagnostic indications. When appropriate it should also define the target population. (When the target population is wider than the clinical trial populations included in the main efficacy studies, this should be justified in the application.)

4.2 Posology and method of administration

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

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 –the Note for Guidance on Clinical Investigation of Medicinal Products in Children : CPMP/EWP/462/95 -), adults, elderly.

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, there should be a recommendation that the medicinal product should not be used in the paediatric age group until further data become available. The reason for the advice should be stated together with any information that may be available on use in paediatric age groups. This additional information could be inserted in sections 5.1 or 5.3.

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

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,
- the intake of the product in relation to food intake.

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 results from clinical studies using cut-off values for biochemical markers of renal impairment, that are defined for specific medicinal product.
- 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,
- 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.

Mention interactions requiring specific dose adjustments.

Short relevant instruction for correct administration/use should also be given here.

In case of restricted medical prescription, specify conditions.

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. absolute contraindications, are the subjects 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 should be specifically avoided (i.e. contraindicated) for concomitant or consecutive use should be stated. Also, where there are strong theoretical reasons (for example, on grounds of pharmacokinetics, pharmacodynamics, or common state of knowledge in medicine) for not using the combination, these should be stated.

In general, patient populations not studied in the clinical trial programme should be mentioned in section 4.4, but 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 patients were actually 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. Under 4.6, a cross-reference should be given and further information about the background should 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).

4.4 Special warning and precautions for use

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. In general, relative contraindications should appear first, followed by warnings and then precautions for use. Patient groups in which use of the medicinal product is absolutely contraindicated should be mentioned under section 4.3 only and not to be repeated here.

Describe:

- the conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled (for example, relative contraindications).
- special patient groups 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, for example, emergency resuscitation.
- when the outcome of an adverse reaction is frequently serious, this could be emphasised by presenting the statement at the top of this section, in bold type, within a box.
- 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 under 4.2 and cross-referenced here.
- clinically relevant interactions where in general the use of the combination should be avoided (relative contraindication) should be mentioned here.
- any warnings necessary for excipients or residues from the manufacturing process.

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

Descriptions of warning 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.

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 outlined here and cross-referenced to the other sections.

Reference to the Note for Guidance on *the Investigation of Drug Interactions* - CPMP/EWP/560/95.

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

a) recommendations : these might be

- contraindication of concomitant use (cross refer to 4.3)
- concomitant use not recommended (cross-refer to 4.4)
- precautions including dose adjustment (cross-refer to 4.2, 4.4), mentioning specific situations where these may be required. For the actual dose recommendation, 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 and

c) mechanism if known

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

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 section 4.2 or 4.4.

Mention should be made in this section of the period of interaction if discontinuation of a medicinal product, which is an enzyme inhibitor or inducer with clinically important interactions, requires adjustment of the doses of concomitant (interacting) medicinal products.

Information on other relevant interactions such as with 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 potentiation or a harmful additive effect, this should be stated. Mention should be made of implications for the need for a washout period when using medicines consecutively. Results demonstrating an absence of interaction should only be mentioned here if this is of likely major interest to the prescriber.

4.6 Pregnancy and lactation

The following should be mentioned :

PREGNANCY

a) Facts on human experience and conclusions from preclinical toxicity studies which are of relevance for the assessment of risks associated with exposure during pregnancy.

b) Recommendations on the use of the medicinal product at different times during pregnancy in respect of gestation.

c) Recommendations on the management of the situation of an inadvertent exposure, where relevant.

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

Relevant details of preclinical studies should be given in section 5.3.

WOMEN OF CHILD-BEARING POTENTIAL

Recommendations on the use of the medicinal product in women of child-bearing potential, when appropriate.

LACTATION

- a) Information on excretion of the active substance and/or its metabolite(s) in milk should be given.
- b) A recommendation as to whether to stop or continue breast-feeding should be given.

FERTILITY

Information regarding fertility should be given in sections 4.3, 4.4, 4.8 or 5.3, as appropriate.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile, reported ADR 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 on all adverse reactions attributed to the medicinal product with at least reasonable suspicion and based 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 be placed before the detailed and specific information presented in the table(s) (see below under 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. It should state what are the most frequently occurring ADRs. Examples of acceptable statements 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)."

or

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

or

"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 table of adverse reactions according to a standard system organ class such as in MedDRA. The system organ classes should be presented in the order shown in Annex 2. Within each system organ class, the ADRs should be ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common ($>1/10$); common ($>1/100$, $<1/10$); uncommon ($>1/1,000$, $<1/100$); rare ($>1/10,000$, $<1/1,000$); very rare ($<1/10,000$), including isolated reports.

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.

More precise frequencies from clinical trials are generally of limited value under conditions of market use. These more precise frequencies, stated as a fraction expressed per 1,000 exposed patients should only be included when it is of particular relevance to the patient and/or prescriber to be informed of certain risks. In these cases it is preferable that the data should be based on pooled study results and/or large studies performed under actual market conditions and should refer to adverse reactions, not to unrelated adverse events.

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", or "Incidence of the adverse reaction considered at least possibly related by the investigator, from clinical trials involving x patients taking the medicinal product" or "Incidence of the suspected adverse reaction in an observational post-marketing study in x patients".

If MedDRA is used, adverse reactions descriptions should be based on the most suitable representation within the 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.

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), (see below), 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, mechanism of the reaction (if of clinical relevance), action to be taken if specific reactions occur (if of particular importance) 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 should be mentioned under 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.

4.9 Overdose

Describe acute symptoms and signs and potential sequela 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.

5 PHARMACOLOGICAL PROPERTIES

Sections 5.1 - 5.3 should only mention information which is relevant to the prescriber 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)
- Mechanism of action (if known)
- Pharmacodynamic effects.
- Clinical efficacy

In general no information is expected. In some cases e.g. in a new therapeutic area, main results (statistically compelling) regarding pre-specified clinically relevant endpoints from major trials, giving the main characteristics of the patient population could be mentioned here in condensed form. This is compulsory for medicinal products approved under exceptional circumstances. (Dir. 75/318/4G)

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.

The primary pharmacokinetic parameters, for instance bioavailability and clearance, should be given as mean values.

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 non-linear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.

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)
- what is the 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.

The information should be presented in a way that enables the prescribing physician to make use of any relevant findings that might apply to the use of the product in patients.

Note: 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 preclinical testing should be described in brief and qualitative statements as outlined in the following example statements:

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

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; for further details on the excipients to be declared, refer to 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.

Excipients should be referred to by their recommended INN if one exists, accompanied by the salt or hydrate form if relevant or by their European Pharmacopoeia name. If an excipient has neither an INN nor Ph. Eur. 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, 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.

Trade 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.

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. 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 Clinical Particulars.

Where studies have not been carried out, and if appropriate for the product, a warning should be included not to mix the product with other medicinal products.

If incompatibilities are not appropriate for the product, e.g., solid oral pharmaceutical forms, the statement ‘not applicable’ should appear.

Biological products (additional)

Relevant chemical/pharmaceutical/biological incompatibilities of the medicinal product with other medicinal products or devices should be addressed.

6.3 Shelf life

- shelf life of the medicinal product as packaged for sale
- shelf life after dilution or reconstitution according to directions
- shelf life after first opening the container.

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.

6.4 Special precautions for storage

Use exact wording of the standard storage warnings given in the Note for Guidance on Declaration of Storage Conditions for Medicinal Products in the Product’s Particulars. If no storage warning is required, state ‘No special precautions for storage’.

For statements to be included regarding storage of sterile products which have been opened, diluted or reconstituted, consult the Note for Guidance on Maximum Shelf Life for Sterile Products for Human Use after First Opening or Following Reconstitution.

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 the same in the SPC, label and package leaflet.

6.5 Nature and contents of container

Reference should be made to the immediate container using the Ph. Eur. 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. measuring spoons, inhaler devices, desiccant. The container of any solvent provided with the medicinal product should also be described.

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 Instructions for use and handling <, and disposal>

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. Only information necessary for the pharmacist or other health personnel to prepare the product for administration to the patient should be included here. Instructions on handling of the product by the doctor, other health personnel, or patient should be included in section 4.2 Posology and Method of Administration.

Claims on compatibilities can be given here provided the data have been provided in the dossier.

In the case of products for reconstitution, the appearance of the product after reconstitution should be stated.

Instructions for disposal should be included here, if appropriate for the product. For radiopharmaceuticals, special instructions relating to the disposal of containers and unused contents should be included.

Additional, for certain products such as cytotoxics and some biological products

Any directions necessary for the accurate preparation of the product and/or necessary for the protection of persons preparing or handling the product should be stated.

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

7. **MARKETING AUTHORISATION HOLDER**

Name and permanent address or registered place of business of the holder of the marketing authorisation. Telephone, fax numbers or e-mail addresses should not be included.

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. Only one date should be included, which should be either the date of first authorisation if the authorisation has not been renewed or the date of (last) renewal.

10. DATE OF REVISION OF THE TEXT

Leave blank in case of a first 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.

ANNEX 1

1. [Generic name] causes/is suspected to cause serious birth defects when administered during pregnancy.

[Tradename] is contraindicated (only in case of a strict contraindication see 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.

[Tradename] 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.

[Tradename] 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. [Tradename] 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) 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