ETHIOPIAN FOOD AND DRUG AUTHORITY

Guideline for Medicinal product information

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Contents

Acronyms

- **“Invented name**”: means the trade name of a medicine.
- **“INN”:** international nonproprietary name
- “**PIL**” : Patient information leaflet
- **“SmPC”:** Summary of product characteristics

Acknowledgments

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Definitions

Active substance

Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

Adverse reaction

A response to a medicinal product which is noxious and unintended occurs at doses normally used.

Approve or "approval"

Means official consent by the Authority as an acceptance of a medicinal product or practices related to that medicinal product to circulate in the Ethiopian market.

Authority

Means the Ethiopian Food and Drug Authority or in its acronym "EFDA"

Batch number" or "**lot number**"

Means a unique number or combination of numbers or cyphers allocated to a lot or a batch by the manufacture';

Common name

The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name;

Excipient

Any constituent of a medicinal product other than the active substance and the packaging material

Immediate packaging

The container or other form of packaging immediately in contact with the medicinal product

Labeling

Any printed, stenciled marked, embossed or impressed text or graphic matter on the immediate container, on the outer pack, any other printed material supplied together with the medicinal product and including patient information leaflet.

Labeling insert"/"**Package insert**"/ "**Package leaflet**"/"Patient information leaflet

A leaflet containing information for the user or patients which accompanies the medicinal product

Manufacturer

Means a person or a firm that is engaged in the manufacture of medicinal products;

Marketing authorization

Means an official approval of the medicinal product to be marketed or distributed in Ethiopia.

Outer packaging

The packaging into which immediate packaging is placed.

Radiopharmaceutical

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

Strength of the medicinal product

The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.

Summary of product characteristics

Is a legal document approved as part of the marketing authorization of each medicine and the basis of information for healthcare professionals on how to use the medicine.

Person

Means a natural and juridical person and Any expression in the masculine gender shall also apply to the feminine gender

Background

Medicinal product information plays an essential part in the safe and effective use of the medicine by both the patients and healthcare professionals. Therefore, as it is the right of the professionals and the patient to get the correct and reliable information, it is also necessary to control and deter illegal circulation of unauthorized products and information in Ethiopian market.

Product information is a document providing officially approved information on a medicine for healthcare professionals and patients. This information includes the summary of product characteristics, package leaflet and labeling.

The product assessment report should provide detailed information on the medicinal products and should be available on the Authority's web site and a link to the relevant website should be included when a public reports are published.

This guideline is therefore ,to provide information and guide the applicants on the format and data requirements of EFDA for the preparation of product labeling information ;to provide information to the applicants on the requirements regarding the legibility, format and content of the PIL for use by prescribers and patient; to assist applicants and marketing authorizations holders when drawing up the labeling and package leaflet and preparing the mock-ups or specimens of the sales presentations; to provide guidance on how to ensure that the information on the labeling and package leaflet is accessible to and can be understood by those who receive it, so that they can use their medicine safely and appropriately; to guide assessor how to review the submitted information and write assessment repot to be availed to the professionals, patients and public

The principles setouts in this guideline are applicable to all medicinal products, including Radiopharmaceuticals, vaccines and biological products. The application of those principles for a particular medicinal product will depend on the scientific knowledge on the medicinal product, the legal basis of a marketing authorization and public health needs. Deviation from this guideline should therefore be justified in the relevant Overview or Summary in the marketing authorization application.

Applicants are advised to follow the format stipulated in this guideline and may refer other relevant medicine registration guidelines while compiling product information.

PART I
The General guidance

General guidance on presenting the product information

a. Product information (SmPC & PIL) should be typed using double line spacing.

b. The print quality of the product information should be clear and concise.

c. The product information should be made available in English or in Amaharic.

d. Each section should first deal with those issues that apply to the core population for whom the medicine is indicated. when necessary should be followed by specific information for any relevant special population (e.g. children or elderly).

e. The product label shall include GS1 2D data matrix barcodes as prescribed in Pharmaceutical Products Bar-coding guideline of EFDA.

f. The GS1 Data Matrix barcode shall be encoded with but not limited to GS1 Global Trade Item Number (GTIN), Expiration date, Batch/lot number and Serial number (SN)

g. 2D barcodes on the product's labelling with links to promotional internet websites not allowed.

h. Information provided in the labeling information should be consistent with the information submitted in the product application dossier.

i. If any other foreign language text other than English is included in the label, the applicant must provide an official statement to declare that the foreign text is complete, accurate, contains unbiased information and is consistent with the English text

j. The applicant shall propose a summary of the product characteristics, in accordance with the format presented in part II of this guideline.

k. When the marketing authorization is issued, the Authority shall inform the Market Authorization holder that the product labeling, summary of the product characteristics and Patient information leaflet are approved.

l. The information that appears on the label and leaflet shall be easily legible, clearly comprehensible and indelible.

m. The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required for the patient information leaflet is directly conveyed on the outer packaging or on the immediate packaging.

n. The draft artworks, specimens or mock-ups of outer cartons and primary labels submitted in the dossier should be consistent with the formats, designs and colours of the original labels that would be used on commercial packs to be marketed. Handwritten information on the artworks, specimens, or mockups are not acceptable, with the exception of statements such as "batch number and expiry dates will be printed".

o. The symbols or pictograms on the outer packaging and the package leaflet may be used as an additional measure if they make the message clear to the patient, but shall not include any element of a promotional nature.

p. The approved SmPC, patient information leaflet and label shall be published on the authority's website for the public.

q. After the registration of medicine, the product information (SmPC, package insert and label) shall not be changed without the approval of the Authority.

r. The approved product information may be submitted for variations, a corresponding proposed product information and previously approved once shall be submitted for approval.

s. The package leaflet is well designed and clearly worded; this maximizes the number of people who can use the information, including older children and adolescents, those with poor literacy skills and those with some degree of sight loss.

PART II

GUIDANCE ON FORMAT AND CONTENT OF SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

1. General

The summary of the product characteristics should be structured and populated as outlined in 1-10 below and at least contain the following information.

1) Name of the medicinal product

The (invented) name should be followed by both the strength and the pharmaceutical form.

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.

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 of a medicinal product should be described by a single full Standard Term of the official recognized Pharmacopoeia using the plural form if appropriate (e.g. tablets) (see section 3).

If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms in accordance with the document "Standard Terms,

Introduction and Guidance to use". If this is not be possible, the competent authority should be consulted

No reference should be made to the route of administration or container unless these elements are part of the standard term or where there is a particular safety reason for their inclusion or where there are identical products, which may be distinguished only by reference to the route of administration or to the container.

2) QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) and excipients, knowledge of which are essential for proper administration of the medicinal product, should be provided in section 2 and as appropriate in section 4.3 or 4.4.

For example, excipients listed in the Annex to the "Guideline on the excipients in the label and package leaflet of medicinal product for human use" should be stated here under a separate subheading qualitatively, and, quantitatively.

For certain excipients, information does not need to be included in section 2,but does need to be included in section 4.4, for example if a product contains less than 1 mmol of sodium per dose. In this case, the amount of sodium does not need to be listed in section 2, and the following statement in section 4.4 will suffice.

This medicinal product contains less than 1 mmol of sodum (23mg) per *<dose>, i.e. is essentially 'sodium-free).*

However, if the product contain more than 1 mmol of sodum per dose, the amount of sodium must be mentioned in section 2, and the following statement should be included in section 4.4: This medicinal product contains x mmol(or y mg) of sodium per *<dose>. Care is required in patients with a sodium-restricted diet).*

The following standard statement should be included at the end of the section, i.e. 'for full list of excipients, see section 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

a. The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

b. If no INN exists, the official recognized 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.

c. Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared.

d. References to the pharmacopoeial quality should not be included.

e. 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 should 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 should be related to the declaration of strength in section 1.

Quantity should be expressed in internationally recognized standard term which could be complemented with another term if more meaningful to healthcare professionals.

a. 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 moiety (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 the preparation of the finished product (i.e. formed during the mixture of a solvent and powder), the quantity of the active moiety 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 term of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed in situ.

b. 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 moiety 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 moiety (e.g. 75 mg of fosphenytoin is equivalent to 50 mg of phenytoin).

c. Oral powders for solution or suspension

For Oral powders for solution or suspension, the quantity of active substance 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.

d. Parenterals excluding powders for reconstitution

For single-dose parenterals (excluding powders for reconstitution), 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 (excluding powders for reconstitution), 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 (excluding powders for reconstitution), the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml, etc. as appropriate, except for multi-dose 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 milli-moles. For X-ray contrast media with iodine-containing actives substances, the quantity of iodine per ml should be stated in addition to the quantity of the active substance.

e. 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.

f. 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.

g. *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'.

h. 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 medicinal products

Expression of strength

The quantity of biological medicinal products should be expressed in terms of mass units, units of biological activity, or International Units as appropriate for the particular product, and reflecting European Pharmacopoeia usage where relevant. For pegylated proteins, the Committee for Medicinal Products for Human Use (CHMP) Guideline on the Description of Composition of Pegylated (Conjugated) Proteins in the SmPC should be referred to.

The biological origin of the active substance

The origin of the active substance should be defined briefly. Thus, the nature of any cellular system(s) used for production and, if relevant, the use of recombinant DNA technology should be specified. The entry should take the form: "produced in XXX cells ". The following are examples of the application of this principle:

"produced in human diploid (MRC-5) cells",

"produced in Escherichia coli cells by recombinant DNA technology",

"produced in chick-embryo cells",

"produced from the plasma of human donors",

"produced from human urine",

"produced from blood",

"produced from porcine pancreatic tissue",

"produced from porcine intestinal mucosa"

Special provisions for normal immunoglobulins

In the case of normal immunoglobulins, the IgG subclass distribution should be stated in terms of percent of total IgG present. The upper limit of the IgA content should follow.

Special provisions for vaccines

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.

Residues that are of special relevance (e.g. ovalbumin in egg derived vaccines) should be specified.

Additional specific guidance is available in CHMP guidelines on biotechnological medicinal products, e.g. the CHMP Guideline on the Pharmaceutical Aspects of the Product Information for Human Vaccines.

3) PHARMACEUTICAL FORM

a. The pharmaceutical form should be described by a full standard term of the EFDA recognized Pharmacopoeia using the singular form.

b. The term used in this section should be the same as the term used in section 1.

c. A visual description of the appearance of the product (colour, markings, etc.) should be given, in a separate paragraph to the standard term, including information on the actual size of a solid oral formulation, e.g. 'White, circular flat beveled-edge tablets of 5 mm marked '100' on one side'

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

e. Information on pH and osmolarity should be provided, as appropriate.

f. In case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. But the appearance of the product after reconstitution should be stated in sections 4.2 and 6.6.

4) CLINICAL PARTICULARS

4.1. Therapeutic indications

a. 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.

b. When appropriate it should define the target population especially when restrictions to the patient populations apply.

c. Study endpoints should not normally be included, unless such mention is specified as being appropriate for the indication. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

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

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

f. It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated for use by <adults><><infants><children under age of 1>< children ><adolescents><aged x to y><years, months>.

g. If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication.

4.2. Posology and method of administration

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

In case of specific safety need, any recommended restriction to a particular setting should also be stated (e.g. "restricted to hospital use only" or "appropriate resuscitation equipment should be available").

If it has been demonstrated that taking the food has no effect on the product, the following standard statement may be included:

"the efficacy of {product name} is not affected by the intake food.{ product name } may be taken before, during or after the meal}.

If there may not be any information available for older products in particular, unless otherwise demonstrated, the following statement should be included:

" it is unknown whether the efficacy of [Product name] is affected by the intake of food. "[Product name] should be taken before a meal,)

Posology

The dosage should be clearly specified for each method/route of administration and for each indication, as appropriate.

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

Dose recommendations (e.g. mg, mg/kg, mg/m2) should be specified per dose interval for each category where appropriate (specify age/weight/body surface area of subsets of the population as appropriate).

Frequency of dosing should be expressed using time units (e.g. once or twice daily or every 6 hour) and, to avoid confusion, abbreviations e.g. OD or BID should not be used.

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, or e.g. in case of vomiting (the advice should be as specific as possible, taking into consideration the recommended frequency of dosing and relevant pharmacokinetic data)
- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of anti-emetics) with cross-reference to section 4.4,
- the intake of the product in relation to drink and food intake, together with a cross-reference to section 4.5 in case of specific interaction e.g. with alcohol, grapefruit or milk,
- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate,
- interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SmPC (e.g. 4.4, 4.5, 4.8, 5.1, 5.2), and
- it may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dosetitration.
- Where relevant to the particular product, the following should appear 'The potency of this medicinal product is expressed in units. These units are not interchangeable with the units used to express the potency of other preparations'.

Special populations

Dosage adjustments or other posology related information in specific patient groups should be stated where necessary, in well-defined sub-sections ordered by importance, e.g. regarding:

elderly population; it should be made clear whether or not any dosage adjustment is necessary in any subsets of the elderly population, with cross-reference to other sections providing information in elderly, e.g. 4.4, 4.5, 4.8 or 5.2.

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

hepatic impairment, 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;

patients with a particular genotype; with cross-reference to other relevant sections for further detail as appropriate;

other relevant special population (e.g. patients with other concomitant disease or overweight patients).

Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms and signs, and/or laboratory investigations, including blood concentrations of the medicinal product should be mentioned when appropriate with cross-reference to other sections where appropriate.

Paediatric population

The specific sub-section 'paediatric population' should always be included and the information given should cover all subsets of the paediatric population, using a combination of the possible situations presented below as appropriate.

If the product is indicated in the paediatric population, posology recommendations should be given for each of the relevant subsets. The age limits should reflect the benefit-risk assessment of the available documentation for each subset.

If the posology is the same in adults and children, then a statement to this effect is sufficient; the posology does not need to be repeated.

Dose recommendations (e.g. mg, mg/kg, mg/m2) should be specified per dose interval for the paediatric subsets where the product is indicated. Different subsets may require different dosing information. If necessary, recommendations in preterm newborns should be presented taking into account the more appropriate age e.g. gestational age or the post-menstrual age.

Depending on the subset, the clinical data and available formulations, the dose will be expressed according to weight or body surface area, e.g. "children aged 2-4 years, 1 mg/kg bodyweight twice a day".

When appropriate, information on timing of intake of the product should consider children's daily life, e.g. school or sleep.

Where a product is indicated in children and no adequate pediatric formulation can be developed, detailed instructions on how to obtain an extemporaneous preparation shall be included in section 6.6 with a cross-reference in section 4.2.

Doses and method of administration in the various subsets may be presented in a tabulated format.

If there is no indication for the product in some or all subsets of the pediatric population, no posology recommendation can be made, but available information should be summarized using the following standard statements (one or combination of several as appropriate):

- The <safety><and><efficacy> of X in children aged xto y <months,years><or any other relevant subsets e.g.weight, pubertal age, gender><have><have>not><yet>been established.

One of the following statements should be added:

– <No data are available> or

–<Currently available data are described in section <4.8><5.1><5.2> but no recommendation on a posology can be made >

- X should not be used in children aged x toy<years, months<or any other relevant subsets e.g. weight, puberal age, gender>because of<safety><efficacy> concern(s)<concern(s) to be stated with cross-reference to sections detailing data (e.g.4.8 or 5.1)> .
- There is no relevant use of X in<pediatric population><in children aged x to y><years, months><or any other relevant subsets. e.g. weight, pubertal age, gender> in the indication(s)<specify indication(s)>.
- X is contraindicated in children aged x to y<years, months><or any other relevant subsets e.g. weight, pubertal age, gender><in the indication…..>(cross-reference to section 4.3).
- If there are more appropriate strength(s) and/or pharmaceutical form(s) for administration in some or all subsets of the paediatric population (e.g. oral solution for infants), these can be mentioned in section 4.2 of the SmPC of the less appropriate one(s).

  E.g.: Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Method of administration

Any special precautions related to the manipulation or administration of the product (e.g. cytotoxic products) by healthcare professionals (including pregnant healthcare professionals), the patient or carers should be mentioned here under a specific sub-heading (), with a cross-reference to section 6.6 (or 12).

The route of administration and concise relevant instruction for correct administration and use should be given here. Information on instructions for preparation or reconstitution should be placed in section 6.6 'Special precautions for disposal of a used medicinal product and other handling of the product' (or in section 12 if appropriate) and cross-referenced here.

When supportive data are available, information on alternative method(s) to facilitate administration or acceptability should be given as explicitly as possible (e.g. possibility of crushing tablet, cutting tablet or transdermal patch, pulverising tablet, opening capsules, mixing with food, dissolution in drinks – specifying if a proportion of the dose can be given) particularly for administration via feeding tubes.

Any specific recommendation for use related to the pharmaceutical form should be explained, e.g.:

- "the coated tablet should not be chewed because of,

- "the enteric-coated tablet should not be crushed because coating prevents on the gut",

- "the coated tablet should not be broken because the coating is intended to ensure a prolonged release (see 5.2)".

For parenteral formulations, information on the rate or speed of injection or infusion should be provided. For parenteral formulations - in children, especially newborns in whom quite often fluids have to be restricted - it would be useful to have information on maximal concentration that can be safely administered (e.g. "no more than X mg of Y/ml of solution").

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

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

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 eliminated substances with narrow therapeutic margin in renal failure patients). If, however, patients have been excluded from studies due to a contraindication on grounds of safety, they should be mentioned in this section. If applicable a cross-reference to section 4.4 should be made.

Only if pregnancy or breastfeeding is contraindicated, should it be mentioned here. In section 4.6, a cross-reference should be made and further background information provided.

Hypersensitivity to the active substance or 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.

Lack of data alone should not lead to a contraindication. Where for safety reasons, the product should be contraindicated in a specific population, e.g. paediatric or a subset of the paediatric population, it should appear in this section with a cross-reference to the section giving detailed information on the safety issue. A contraindication in the paediatric population should be listed without a sub-heading.

Mention of 'Pregnancy' as a contraindication should only occur under very specific circumstances, namely in case of demonstrable human risk. This means an 'absolute' contraindication, which makes use of the product during pregnancy irresponsible due to expected harmful effects for the foetus. A contraindication based solely on the fact that evidence from animal studies is lacking is not permitted, as this is confusing.

If the simultaneous use with a certain group of medicinal products is contraindicated, inclusion of only the group or class of medicinal products in this section, with a reference to section 4.5, is sufficient. The list of all the active substances that fall within the contraindicated group/class can be provided in section 4.5. However, section 4.5 should clearly state that this refers to contraindicated simultaneous use, with a reference to section 4.3.

4.4. Special warnings and precautions for use

The order of warnings and precautions should in principle 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. Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk. 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 following should be described:

- The conditions, in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled. In particular, specific risk minimisation measures requested as part of a Risk Management Plan to ensure safe and effective use should be described in this section. (For example; “Liver function should be monitored before initiation of treatment and monthly thereafter”, “Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation”, “Women of childbearing potential should use contraception”, …)
- Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions (usually serious or common), e.g. elderly, children, patients with renal or hepatic impairment (including the degree of impairment, e.g. mild, moderate or severe), patients having an anaesthesic or patients with cardiac failure (including in this case the NYHA Classification for example). Cross-reference to section 4.8 on the differential effects in terms of frequency and severity of the specified adverse reaction should be provided.
- Serious adverse reactions to which healthcare professionals need to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.
- If serious adverse reactions have been reported for a medicinal product when used for an un-authorised indication (so-called off-label use), the following statement should be included in section 4.4: *(*Cases of ... (severe adverse reactions) have been reported following use of X for the un-authorised indication...)

- 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 adverse reaction, a statement should be included.
- Any need for specific clinical or laboratory monitoring should be stated. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice. If dose reduction or other posology is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.
- Any warnings necessary for excipients or residues from the manufacturing process.
- For herbal preparations containing alcohol, information about the ethanol content in the medicinal product should be included in accordance with the Guideline on excipients in the label and package leaflet of medicinal products for human use.
- Any warnings necessary with respect to transmissible agents (e.g. Warning of Transmissible Agents in SmPCs and Package Leaflets for Plasma-Derived Medicinal Products (CPMP/BPWG/BWP/561/03).
- Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known.

- Any particular risk associated with an incorrect route of administration (e.g. necrosis risk with extravasation of intravenous formulation, or neurological consequences of intravenous use instead of intramuscular use), should be presented, with advice on management if possible.
- 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 should also be included in section 4.8.
- Specific interference with laboratory tests should be mentioned when appropriate, e.g. Coombs test and Beta-lactams. They should be clearly identified with a subheading, e.g. “Interference with serological testing”.
- In general, descriptions of warnings and precautions regarding pregnancy and breast-feeding, 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. However in specific cases of major clinical importance it might be more appropriate to describe specific precautionary measures in this section, e.g. contraception measures, or when concomitant use of another medicine is not recommended, and with cross reference to section 4.5, 4.6, or 4.7.

Paediatric population

When the product is indicated in one or more subsets of the paediatric population and there are warnings and precautions for use that are specific to the paediatric population or any subset of the paediatric population, they should be identified under this subheading. Any necessary warning or precaution in relation to long-term safety (e.g. on growth, neuro-behavioural development or sexual maturation) or specific monitoring (e.g. growth) in the paediatric population should be described. When long-term safety data are necessary but not yet available, it should be stated in this section. Warnings should be included in case of possible significant or long-lasting impact on children's daily activities, such as learning ability or physical activities, or in case of impact on appetite or sleep pattern.

If measures are requested that are specific to the paediatric population for which the product is indicated (e.g. as part of a Risk Management Plan), these measures should be described in this section.

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 SmPC 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 or 4.4, as appropriate), mentioning specific situations where these may be required. b.

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. For example, interaction due to inhibition or induction of cytochrome P450 should be presented as such in this section, with a cross-reference to 5.2 where in vitro results on inhibition or induction potential should be summarised.

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, crossreferring 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, alcohol, smoking, 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.

In vivo results demonstrating an absence of interaction should only be mentioned here if this is of major importance to the prescriber (e.g. in therapeutic area where potentially problematic interactions have been identified such as with anti-retroviral medicines).

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 interactions with other medicinal products depend on polymorphisms of metabolising enzymes or certain genotypes, this should be stated.

Pediatric population

Information specific to a subset of the paediatric population should be given here if there is an indication for the particular age group.

The resulting exposure and clinical consequences of a pharmacokinetic interaction can differ between adults and children, or between older and younger children. Therefore;

• Any identified treatment recommendations should be given in relation to concomitant use in the paediatric subset(s) (e.g. dose adjustment, extra-monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring),

• If the interaction studies have been performed in adults, the statement ‘Interaction studies have only been performed in adults’ should be included.

• If the extent of an interaction is known to be similar in a paediatric age group to that in adults, this should be stated.

• If this is not known, this should also be stated. The same applies to pharmacodynamic drug interactions.

In cases of food interaction leading to a recommendation on co-administration with a meal or specific food, it should be specified whether this is relevant for paediatric use (especially newborns and infants) whose diet is different (100 % milk in newborns).

In the event of interactions with food, a cross-reference to sections 4.2 and 5.2 should be included.

Overall, section 4.5 should be presented in the simplest possible way to highlight the interactions resulting in a practical recommendation regarding the use of the medicinal product. Presentation in a tabulated format may help where interactions are numerous and various, such as with anti-viral products.

4.6. Fertility, pregnancy and lactation

General principles

Efforts should be made by the Marketing Authorization Applicant or Holder to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential. This information is important for the healthcare professionals informing the patient.

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

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

In case of contraindication, this should be included in section 4.3.

The following should be mentioned:

Women of childbearing potential / Contraception in males and females

Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including the need for pregnancy test or contraceptive measures. Where an effective contraception is required for patients or partners of patients during treatment or for a defined period before starting or after ending treatment, the rationale should be included in this section. If contraceptive measures are recommended, there should also be a cross-reference to section 4.5 (and possibly 4.4) in case of interaction with oral contraceptives.

Pregnancy

In general, clinical and non-clinical data should be followed by recommendations.

With respect to non-clinical data,

- Only conclusions of the reproductive toxicity studies should be included in this section. Further details should be provided in section 5.3. 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) should be specified when available.
- the section should specify the extent of the human experience if no adverse events have been reported in pregnancy.

With respect to the recommendations:

a) Recommendations on the use of the medicinal product during the different periods of gestation, including the reason(s) for these recommendations, should be given.

b) 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 fetus or the neonate) should be given.

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

Examples of wording for this section are annexed to the CHMP/SWP guideline on reproduction and lactation.

Breastfeeding

If available, clinical data should be mentioned (exposed breastfed infants) as the conclusions of kinetic studies (plasma concentrations in breastfed infants, transfer of the active substance and/or its metabolite(s) into human milk…). Information on the degree of excretion on the active substance and its metabolites in breast milk must always be given. It must include a recommendation regarding whether or not breastfeeding may be continued, only needs to be interrupted temporarily (by pumping and disposing of the milk) or needs to be stopped. Data may not be available for older products in particular. This must be stated as such. Conclusions from non-clinical 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.

Recommendations should be given to stop or continue breastfeeding and/or to stop or continue the treatment in cases where treatment or breastfeeding discontinuation is recommended, and the reason should be provided.

Examples of wordings for this section are annexed to the CHMP/SWP guideline on reproduction and lactation.

Fertility

The main information on the possible effects of the medicinal product on male and female fertility should be included in section 4.6.

This section should include:

a) Clinical data if available.
b) Relevant conclusions from nonclinical toxicity studies, if available. 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.

Cross-references could be included in section 4.3, if appropriate.

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

4.7. Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines, specify whether the medicinal product has a) no or negligible influence b) minor influence, c) moderate influence or d) major influence on these abilities. Other important factors that affect the ability to drive and use machines should be considered if known, e.g. duration of the impairing effect and the development of tolerance or adverse reactions with continued use.

For situations c and d, special warnings/precautions for use should be mentioned here (and also in section 4.4 for situation d).

If an effect is unlikely, the following statement may be included: (<x> has no or negligible influence on the ability to drive and use machines.)

4.8. Undesirable effects

This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, 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 case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC.

The content of this section should be justified in the Clinical Overview of the marketing authorisation application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product.

In addition, the whole section could be revised at the renewal of the marketing authorisation, where the safety profile of most products is likely to be well established, and thereafter at each of the three-yearly PSUR.

It is important that the whole section is worded in concise and specific language and does 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 such as "well tolerated", "adverse reactions are normally rare", etc. Statements on lack of proof of causal association should not be included.

In order to provide clear and readily accessible information, section 4.8 should be structured according to the following recommendations:

a) Summary of the safety profile
b) Tabulated summary of adverse reactions
c) Description of selected adverse reactions
d) <Pediatric population>
e) <Other special population(s)>

a. Summary of the safety profile

The summary of the safety profile should provide information about the most serious and/or most frequently occurring adverse reactions.

If known, it may be helpful to indicate the timing when adverse reactions occur. For example, in order to prevent early discontinuation of a treatment, it may be important to inform about non-serious adverse reactions that are frequent in the beginning of the treatment but may disappear with its continuation. Another example would be to inform about adverse reaction associated with long-term use. Frequencies of cited adverse reactions should be stated as accurately as possible. This summary of the safety profile should be consistent with the important identified risks mentioned in the Safety Specification of the Risk Management Plan. The information should be consistent with the Table of Adverse Reactions (see section b). Cross-reference should be made to section 4.4 if relevant risk minimization measures have been proposed in that section.

An example of an acceptable statement is given below:

> 'At the beginning of the treatment, epigastric pain, nausea, diarrhoea, headache or vertigo may occur; these reactions usually disappear within a few days even if treatment is continued. The most commonly reported adverse reactions during treatment are dizziness and headache, both occurring in approximately 6% of patients. Serious acute liver injury and agranulocytosis may occur rarely (less than 1 case per 1,000 patients)'

b. Tabulated list of adverse reactions

A single table (or structured listing) should list all adverse reactions with their respective frequency category. In some cases for common or very common reactions, and when it is necessary for the clarity of the information, frequency figures may be presented in the table.

Separate tables are acceptable in exceptional cases where the adverse reaction profiles markedly differ depending on the use of the product. For example, it might be the case for a product used for different indications (e.g. an oncology and a non-oncology indication) or at different posologies.

The table should be introduced with a short paragraph stating the source of the safety database (e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting).

The table should be presented according to the MedDRA system organ classification. The system organ class (SOC) should be presented in the order shown in the annex. Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) 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 adverse reactions should be assigned to the most relevant SOC related to the target organ. For example, PT 'Liver function test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'. Within each system organ class, the adverse reactions should be ranked under headings of frequency, most frequent reactions first. Within each frequency grouping, adverse reactions should be presented in the order of decreasing seriousness. The names used to describe each of the frequency groupings should follow standard terms established in each official language using the following convention: Very common (≥1/10); common (≥1/100 to<1/10);uncommon (≥1/100);rare(≥1/10,000 to<1/1000);very rare (<1/10,000).

In exceptional cases, if a frequency cannot be estimated from the available data, an additional category frequency 'not known' may be used. In case the expression "Frequency not known" is used, the following text should be added in the list of terms explaining the frequency categories: "not known (cannot be estimated from the available data)". The expressions isolated/single cases/reports should not be used.

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.

Guidance on how to estimate the frequency of an adverse reaction is provided at the end of this chapter of the guideline.

c. Description of selected adverse reactions

This section should include information characterizing specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice.

This section should include information characterizing individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information should provide frequency and may describe for example reversibility, time of onset, severity, duration, mechanism of the reaction (if of clinical relevance), dose

relationship, relationship with duration of exposure or risk factors. Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur should be mentioned under section 4.4 and cross-referenced here.

Information on the occurrence of withdrawal reactions may be mentioned here with cross-reference to section 4.2 in case of need for tapering off or advice on discontinuation of the product.

Mention should be made here of any differences between different dosage forms in respect of adverse reactions.

In the case of combination products, information should be included in this sub-section pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known.

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

This section should also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned.

Any adverse reaction specific to excipients or residues from the manufacturing process should be included.

d. Pediatric population

A pediatric sub-section should always be included (unless irrelevant).

The extent and age characteristics of the safety database in children should be described (e.g. from clinical trials or pharmacovigilance data). Uncertainties due to limited experience should be stated.

If the observed safety profile is similar in children and adults this could be stated: e.g. “Frequency, type and severity of adverse reactions in children are to be the same as in adults”. Similarly, it is appropriate to state whether the safety profiles in the different paediatric subsets are similar or not.

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and paediatric populations, or in any relevant age groups, should be described and presented by age group. If there is a need for specific monitoring, this should be highlighted by cross-referencing to section 4.4. For clinically relevant differences, a separate table listing such adverse reactions by frequency can be added and presented by relevant age groups if appropriate. If some paediatric adverse reactions are considered common (≥1/100 to long-term safety in children (e.g. on growth, mental development and sexual maturation) should also be summarized, whether positive or

negative, with cross-reference to section 5.1 if appropriate. Any risk factors such as duration of treatment or period at risk should be specified.

If relevant, symptoms of neonatal withdrawal should be listed in a separate paragraph with cross reference with 4.6.

e. Other special populations

This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate. Adverse reactions may also be related to genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials.

Further guidance on the estimation of frequency of adverse reactions

The estimation of the frequency of an adverse reaction depends on the data source (i.e. clinical trial, post-authorisation safety study or spontaneous reporting), the quality of data collection and causality evaluation. If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless a more specific method has been applied and thus resulted in an estimate of clearly higher validity, e.g. a pooled analysis across suitable studies.

Sources of data should use population exposed to the doses and treatment duration as recommended in the SmPC.

Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, reactions that represent a syndrome complex should ordinarily be grouped together under an appropriate heading to avoid obscuring the full range of respective symptoms.

Adverse reactions from clinical trials

Safety data from several studies should be pooled to increase the precision of adverse reaction rates as appropriate without introducing bias (e.g. major difference in population characteristics or exposure to the product).

The frequency of adverse reactions should be derived from pooled placebo-controlled studies if these data are available and the databases are sufficiently large to be informative. If these data are unavailable or not sufficiently informative, active-controlled data or possibly single-arm or add-on trials databases could be used to estimate frequencies. Frequency should

represent crude incidence rates (and not differences or relative risks calculated against placebo or other comparator).

When a common, very common or serious adverse reaction (e.g. suicide) also occurs in the placebo group with a relevant frequency, both incidence rates can be stated to put the risk into perspective (e.g. in subsection c).

Adverse reactions from safety studies

The choice of the frequency category to which any adverse reaction will be assigned is based on the point estimate of the crude incidence rate derived from a study designed in such a way that specific adverse events occurring in patients within a defined observation period would have been detected and reasonably attributed to the medicinal product. In this situation, it is possible to calculate a point estimate of the crude incidence rate using standard statistical methods. In cases where the original information is expressed as an incidence density (denominator expressed as person-time), an appropriate transformation into an incidence proportion should be performed for choosing the frequency category. Normally, incidence proportions for the most representative exposure period (e.g. 1 week, 3 months, 1 year) should be used to derive the frequency category. However, this may not be appropriate if the hazard function increases over time; in this case, the adverse reaction and its frequency pattern, when clinically relevant, should be properly described in section c).

The frequency category to be chosen for each adverse reaction should not be based on differences calculated against a comparator. However, when data are derived from a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline or background incidence rate, and if the adverse reaction is considered important, the background incidence may be provided (e.g. in section c).

Adverse reactions from spontaneous reporting

The number of spontaneous reports should not be stated because the number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should not be used to assign frequency category. In case of an unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this adverse reaction could have been detected should be reviewed to choose a frequency category. If the adverse reaction has never been observed in clinical trials, then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies (e.g. those with a follow-up long enough to detect the adverse reaction). For example, if a particular adverse reaction has not been observed among 3600 subjects exposed to the product in clinical trials and studies, then the upper limit of the 95% confidence interval for the point estimate is 1/1200 or less and the frequency category should be "rare", based on worst value of the point estimate. The rationale for the frequency category for that particular reaction could be explained in sub-section c).

4.9. Overdose

This pertains to 'acute' overdose. Chronic overdose and its effects should be listed under section 4.4, insofar as relevant. If an accidental overdose (e.g. oral intake of topical dosage forms by children) can lead to problems, the information about this should be included in this section.

Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on all available information including accidental intake, mistakes and suicide attempts by patients.

Taking into account all relevant evidence, describe management of overdose in man, e.g. in relation to monitoring or use of specific agonists/antagonists, antidotes or methods to increase elimination of the medicinal product such as dialysis. However, there should not be any dosage recommendation of other medicinal products (e.g. antidotes) as it could create conflict with the SmPCs of those other products. If applicable, counteractive measures based on genetic factors should be described.

Additional information on special populations

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

Paediatric population

If there are specific paediatric considerations, there should be a sub-section entitled ‘paediatric population’. Special mention should be made of those medicinal products/strength of formulation for which ingestion of only one dose unit by children can cause fatal poisoning.

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. The sections should be updated regularly when new information becomes available, especially in relation to the paediatric population.

5.1) Pharmacodynamic properties

Describe:

- Pharmacotherapeutic group and ATC code: Inclusion of the therapeutic subgroup (2nd level of WHO classification) with the 3rd (pharmacological subgroup) or 4th (chemical subgroup) level is recommended. If an ATC code is not yet available, this should be mentioned as ‘not yet assigned’.
- In case of medicinal product authorized as similar biological medicinal product, the following statement will be included:
- << (Invented) Name> is a biosimilar medicinal product. Detailed information is available on the European Medicines Agency website; www.emea.europa.eu>

- 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, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures).

In the exceptional cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations.

Any relevant pharmacogenetic information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.

Pediatric population

The results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented under this sub-heading.

Information should be updated when new relevant information becomes available. Results should be presented by age or relevant subsets. When there are data available, but there is no authorized paediatric indication, data should be presented and a cross-reference should always be made to section 4.2and, as appropriate to 4.3.

In presenting results of studies, particular attention should be given to include the relevant safety data. For exploratory studies, the results of the main endpoints should be given with the main characteristics of the population studied and the doses used.

When they are available, information and results of confirmatory studies should usually supersede and replace those of exploratory studies. For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patient), and the main results regarding pre-specified endpoints should be provided, whether positive or negative. If data are considered inconclusive, this should be stated.

The objective and the main results or the conclusion of any specific clinical safety study should also be given.

[If the EFDA recognized national, regional and international bodies has waived or deferred a pediatric development, the information should be given as follows:]

-For waivers applying to all subsets:

"The {name of EFDA recognized national, regional and international body.Eg WHO} has waived the obligation to submit the results of studies with in all subsets of the pediatric population in. See 4.2 for information on pediatric use."

- For deferrals applying to at least one subset:

"The {name of EFDA recognized national, regional and international body.Eg WHO} has deferred the obligation to submit the results of studies with in one or more subsets of the pediatric population in. See 4.2 for information on pediatric use.

[For products approved under 'conditional approval' in the centralized procedure, include the following statement:]

<This medicinal product has been authorized under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The EFDA will review new information on the product every year and this SmPC will be updated as necessary>.

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

^This medicinal product has been authorized under 'eceptional 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 EFDA will review any new information which may become available every year and this SmPC 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, information on the population in which general pharmacokinetic data were obtained, etc.
b) General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.
    i) Absorption: complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; Tmax; the influence of food; in case of locally applied medicinal product the systemic bioavailability; involvement of transport proteins. If available, information on the site of absorption in the gastro-intestinal

tract should be stated (as it may be important for administration by enteral feeding tubes).

ii) Distribution: plasma protein binding; apparent volume of distribution per kilogram body weight (l/kg); tissue and/or plasma concentrations; pronounced multi-compartment behaviour; involvement of transport proteins.

iii) Biotransformation: degree of metabolism; which metabolites; activity of metabolites and contribution to effect and toxicity; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.

iv) Elimination: elimination half-lives, total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites including the relative portion of the hepatic and renal eliminated fraction, involvement of transport proteins.

v) Linearity/non-linearity: linearity/non-linearity of the pharmacokinetics of the active substance 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.

vi) Additional relevant information should be included here.

c) Characteristics in specific groups of subjects or patients

Variations with respect to factors such as age, weight, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic disease, including degree of impairment. If the influence on pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-reference to section 4.2 when applicable).

d) Pharmacokinetic/pharmacodynamic relationship(s)

i) Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or side effect).

ii) The population studied should be described.

Paediatric population

Results of pharmacokinetic studies in the different paediatric age groups should be summarised, with a comparison to adults if available. If appropriate, the dose producing similar product exposure as in adults could be given. The pharmaceutical form(s) used for pharmacokinetic studies in children should be stated. Uncertainties due to limited experience should be stated.

5.3) Preclinical safety data

Information should be given on any findings in the non-clinical 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 SmPC.

If the results of the non-clinical studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SmPC.

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

- 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 and development.
- 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.

Findings of non-clinical studies relevant for use in the paediatric population, including juvenile animals and peri- or post- natal studies, should be presented with a discussion of their clinical relevance, under a sub-heading if necessary.

<**Environmental Risk Assessment (ERA)**>

Where relevant, conclusions on the environmental risk assessment of the product should be included, 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 prefilled 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 or 4.4 as appropriate.

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 along with the common name of the excipient where they exist and when necessary for proper use, e.g. 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).

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 or is too complex, it may be declared in general terms (e.g. 'orange flavour', 'citrus perfume'). However, any of the components, which are known to have a recognised action or effect, should 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'.

In the case of a product containing a covert marker for the purpose of tracking, tracing and authentication, a general term such as "authentication factor" should be included in the list of excipients instead of the name of the excipient, unless the excipient is one that is known to have a recognised action or effect.

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, in-line filters, 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 and chemical/physical 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

In this section, both the expiry date and the in-use shelf life, if applicable, are mentioned in accordance with this guideline. 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.

Additionally, if different concentrations need to be prepared, e.g. for use in children, the physicochemical stability throughout the entire concentration range should be stated; e.g. "The stability has been demonstrated between x mg/ml and y mg/ml for t hours/days at 25 ºC and 2-8 ºC".

In case of a pediatric indication, if no age appropriate formulation is available for children but an extemporaneous formulation could be prepared from an existing formulation, relevant physicochemical data on storage and stability should be included here with a cross-reference in sections 6.4 and 6.6."

In case of specific temporary storage conditions need to be provided to healthcare professionals or patients, e.g. for the purpose of ambulatory use (e.g. shelf-life 24 months at 2-8°C of which 3 months could be below 25°C), specific additional guidance should be provided as appropriate. Such information should always be based on stability data. In particular, the recommended temperature range and maximum duration of temporary storage should be specified. This guidance may also include the action to be taken after the product has been stored under the temporary storage conditions (e.g. discard immediately).

Statements such as "These data are not recommendations for storage" should not be used.

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.

When a device is supplied together with a medicinal product, the in-use shelf-life of the device should be given where applicable.

If the in-use shelf life is earlier than the expiry date, the following text should be included after the expiry date:

('After opening of the <primary packaging>, this product will expire in <XXXX days/weeks/months>)

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. When such a standard statement is used, an explanation specifying whether the product is sensitive to light and/or moisture should be added.

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

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

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

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 ('glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, syringes inhaler devices, desiccant. The graduation on measuring devices should be explained. 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. For parenteral preparations, when enclosure colour is used to differentiate between the presentations of a product, this should be stated here.

All authorised package sizes must be included, including bulk packaging that is not sold directly to patients but packaged by the pharmacy. An outer box with smaller packs (multi-unit packs for distribution) does not need to be mentioned, however. Therefore, a pot with 500 tablets should be mentioned, but an outer box with 10 packs of 50 tablets should not.

Particularly in mutual recognition procedures, but also in national procedures, not all packages submitted are actually marketed in the Ethiopia. In this case, the standard phrase "Not all packaging sizes may be marketed" should be included. This does not require further specification.

If appropriate, it should be indicated if the container closure is child-resistant.

Examples on the text in this section:

> <Volume> ml suspension in a pre-filled syringe (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 product[2]

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

Where special precautions for the handling and 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 nappies, or spoons used to administer oral vaccines. If relevant, a cross-reference to conclusions on the environmental risk assessment described in section 5.3 can be included.

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 uses 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 including parents or carers 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.

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.

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, parents or carers). 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.

In the exceptional cases where a product is indicated in children and where no adequate paediatric formulation can be developed (based on duly justified scientific grounds), information on extemporaneous formulation should appear under a sub-heading "Use in the paediatric population" and should cross-refer to the section 4.2. Detailed instructions for the preparation of the extemporaneous formulation from the appropriate "adult" or other "older children" dosage form and additional information on extemporaneous formulations for use in younger children shall be provided and, where appropriate, the maximum storage time during which such preparation will conform to its specifications. When necessary, the required packaging material and storage conditions should be stated here.

Any specific warnings for the handling of the product should be in section 4.4.

Information on risks due to occupational exposure should be included in this section, with reference to section 4.4 or 4.8 if there is information in that section.

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 (not 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 latest 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 SmPC, implementation date of the Urgent Safety Restriction or date of (EMEA) notification amending the annexes to the Marketing Authorization.

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

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.

PART III

GUIDANCE ON FORMAT AND CONTENT OF LABELS FOR MEDICINAL PRODUCTS

1. General requirements for Package leaflets

1) All medicinal products placed on the Ethiopian market are required to be accompanied by labeling and package leaflet which provide a set of comprehensible information enabling the use of the medicinal product safely and appropriately.
2) The particulars to be included in the labeling shall be easily legible, clearly comprehensible and indelible.
3) One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the competent authority at the time of marketing authorization application. The results of assessments carried out in cooperation with target patient groups shall also be provided.
4) The labeling and package leaflet shall appear in Amharic or English.
5) The insert labeling of medicine that is included in the national essential medicine list or widely circulated in the market shall be in Amharic and in English. If the intended distribution of the medicine is limited to one region, its insert labeling shall be, at least, in English and the region's working language. The use of "justified" text (that is text aligned to both left hand and right hand margins) should in principle not be used.
6) Line spaces should be kept clear. The space between lines is an important factor influencing the clarity of the text. The space between one line and the next should be at least 1.5 times the space between words on a line, where practical.
7) Related information should be kept together so the text flows easily from one column to the next. Consideration should be given to using a landscape layout which can be helpful to patients.
8) Where a multilingual leaflet is proposed there should be a clear demarcation between the different languages used; all the information provided in each language should be assembled.
9) Same level headings should appear consistently (numbering, bulleting, colour, indentation, font and size) to aid the reader.
10) The use of multiple levels of headings should be considered carefully, as more than two levels may make it difficult for readers to find their way around the leaflet. However, where complex information has to be communicated multiple levels of headings may be needed.
11) Sub-headings and associated text within the leaflet should only be included if these are relevant for the particular medicine. For example if there is no information in

relation to excipients of known effect this section may be omitted from the package leaflet.

12) There should be a separate PIL for different pharmaceutical forms(eg.Oral and Injectable).

13) Use of long sentences in the leaflet

a) Some people may have poor reading skills, and poor health literacy. Long sentences should not be used. It is better to use a couple of sentences rather than one longer sentence, especially for new information.

b) Long paragraphs can confuse readers, particularly where lists of side effects are included. The use of bullet points for such lists is considered more appropriate. Where possible, no more than five or six bullet points in a list are recommended.

14) Setting out the side effects in the leaflet

a) When setting out the side effects it is particularly important to consider the order in which they are given so the patients/users may maximise the use of the information.

b) setting out the side effects by frequency of occurrence, starting with the highest frequency, is recommended to help communicate the level of risk to individuals.

c) Frequency terms should be explained in a way patients/users can understand – for example “very common” (more than 1 in 10 patients).

d) Where a serious side effect exists which would require the patient/user to take urgent action this should be afforded greater prominence and appear at the start of the section.

e) Setting side effects by organ/system/class is not recommended since patients/users are in general not familiar with these classifications.

15) **Writing style**

a) When writing, an active and direct style should be used, by placing the verb at the beginning of the sentence instead of passive. For example: - 'take 2 tablets' instead of '2 tablet should be taken',' - 'you must....' is better than 'it is necessary ...'

b) When telling patients what action to take, reasons should be provided. Instructions should come first, followed by the reasoning, for example: ‘take care with X if you have asthma – it may bring on an attack’.

c) “Your medicine, this medicine, etc.” should be used rather than repeating the name of the product, as long as the context makes clear what is being referred to.

d) Abbreviations and acronyms should not usually be used unless these are appropriate. When first used in the text, the meaning should be spelled out in full. Similarly scientific symbols (e.g. > or<)are not well understood and should not be used.

e) Medical terms should be translated into language which patients can understand.

f) Consistency should be assured in how translations are explained by giving the lay termwith a description first and the detailed medical term immediately after.

g) On a case by case basis the most appropriate term (lay or medical) may then be used thereafter throughout the package leaflet in order to achieve a readable text.

h) Make sure that the language used alerts the reader to all the information relevant to him/her, and gives sufficient detail on how to recognize possible side effects and understand any action which may be necessary.

16) **Paper used**

a) The paper weight chosen should be such that the paper is sufficiently thick to reduce transparency which makes reading difficult, particularly where the text size is small.

b) Glossy paper reflects light making the information difficult to read, so the use of uncoated paper should be considered.

c) Make sure that when the leaflet is folded the creases do not interfere with the readability of the information.

17) **Use of symbols and pictograms**

a) The use of images, pictograms and other graphics is allowed to aid comprehension of the information, but these exclude any element of a promotional nature.

b) Symbols and pictograms can be useful provided the meaning of the symbol is clear and the size of the graphic makes it easily legible.

c) They should only be used to aid navigation, clarify or highlight certain aspects of the text and should not replace the actual text. Evidence may be required to ensure that their meaning is generally understood and not misleading or confusing.

d) If there is any doubt about the meaning of a particular pictogram it will be considered inappropriate.

e) Particular care will be needed when symbols are transferred or used in other language versions of the leaflet and further user testing of these may be necessary.

18) Products administered by a healthcare professional or in a hospital

a) For a product administered by a healthcare professional, information from the summary of product characteristics for the healthcare professional (e.g. the instructions for use) could be included at the end of the patient leaflet e.g. in a tear-off portion, to be removed prior to giving the leaflet to the patient.

b) Alternatively, the complete summary of product characteristics could be provided in the pack along with the package leaflet.

c) For a product administered in hospital additional package leaflets (in addition to the one provided in the pack) may be made available on request to ensure that every patient receiving the medicine has access to the information.

2. Product labeling

General principles

Labeling covers both outer packaging and inner packaging. Although inner packaging may include a lesser set of particulars, many of the principles outlined in relation to outer packaging will apply equally to the labeling of blister packs or other small package units.

Labeling ensures that the critical information necessary for the safe use of the medicine is legible, easily accessible and that users of medicines are assisted in assimilating this information so that confusion and error are minimized.

Those involved in the design of labeling should consider the following sections prior to submission to the competent authority. The recommendations given in relation to the package leaflet may be applicable to labeling and should be borne in mind in designing and laying out the required information on labels. The particulars appearing on the label of all medicinal products should be printed in characters of at least 7 points (or of a size where the lower case "x" is at least 1.4 mm in height), leaving a space between lines of at least 3 mm.

Labeling must contain the following elements required for the safe use of the medicine.

a) The name of the product– brand and generic/International Non-proprietary Name (INN);

b) Pharmaceutical form and route of administration;

c) Qualitative and quantitative composition of active ingredient(s) and Special excipients such as lactose, Aspartame, preservative(s), and antioxidant (s);

d) The volume of the contents, and/or the number of doses, or quantity in container;

e) Directions to consult the package insert or the carton label for complete directions for use;

f) Handling and storage conditions;

g) License number of the manufacturer;

h) Batch number;

i) Manufacturing date(optional);

j) Expiry date; and,

k) Name and address of manufacturer.

When the immediate container label is too small (in size) to contain all the above information, the label needs to contain at least information as indicated on a, b, c, d, f, h, i and j. Additionally, the label needs to contain logo of the manufacturer and/or license holder.

ANNEX I: SUMMARY OF PRODUCT CHARACTERISTICS

(With proposed sentence patterns and illustrative examples)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

{(Invented) name of product <strength><pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For excipients, see 6.1.

This include the quantitative composition of special excipients (such as Lactose, Aspartame, Preservative and Antioxidants)

3. PHARMACEUTICAL FORM

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<This pharmaceutical product is for diagnostic use only. >

4.2. Posology and method of administration [*See example below*.]

Adults

Children and adolescents (4 to 17 years of age)

General administration recommendations

Special dosing considerations in adults

4.3. Contraindications

<Hypersensitivity to the API(s) or to any of the excipients <or {residues}>

4.4. Special warnings and special precautions for use [*See example below*.]

Drug interactions

Acute hemolytic

Hyperglycemia

Patients with coexisting conditions

4.5. Interaction with other FPPs and other forms of interaction [*See example below*.]

Rifabutin)

Ketoconazole)

Itraconazole)

Nevirapine)

HMG -CoA reductase inhibitors)

Rifampicin)

4.6. Pregnancy and lactation [*See example below*.]

Use during pregnancy)

Use during lactation)

4.7. Effects on ability to drive and use machines

< {Invented name} has <no or negligible influence><minor or moderate influence><major influence> on the ability to drive and use machines.> [describe effects where applicable]

<No studies on the effects on the ability to drive and use machines have been performed.><Not relevant.>

4.8. Undesirable effects [*See example below*.]

Laboratory test findings)

Post-marketing experience)

4.9. Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: {group}

ATC code: {code}

Mechanism of action

Microbiology (when applicable)

Drug resistance (when applicable)

Cross resistance (when applicable)

Pharmacodynamic effects

Adults

Pediatric patients

5.2. Pharmacokinetic properties

Absorption

Distribution

Biotransformation

Elimination

Characteristics in patients

5.3. Preclinical safety data

<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.>

Mutagenicity

Carcinogenicity

Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients [*See example below*.]

Capsule content)

Capsule shell)

Printing ink)

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>

<This pharmaceutical product must not be mixed with other pharmaceutical products except those mentioned in 6.6.>

6.3. Shelf life

<...><6 months><...><1 year><18 months><2 years><30 months><3 years><...>

6.4. Special precautions for storage

<Do not store above <25°C> 30°C»

<Store at 2°C - 8°C (in a refrigerator» <Store in a freezer>

<Do not <refrigerate><or><freeze»

<Store in the original <package><container» <Keep the container tightly closed>

<Keep the container in the outer carton>

<No special precautions for storage>

<in order to protect from <light><moisture»

6.5. Nature and contents of container

<Not all pack sizes may be marketed.>

6.6. Instructions for use and handling <and disposal>

<No special requirements.>

7. MARKETING AUTHORISATION HOLDER

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT