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MINISTRY OF HEALTH

PHARMACY AND POISONS BOARD

GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET, AND LABELLING

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ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
CEP	Certificate of Suitability to the monograph of Ph Eur Monograph
CTD	Common Technical Document
EAC	East Africa Community
EAMRH	East Africa Medicines Registration Harmonization
EA-PSNMRA	East Africa Partner State National Medicines Regulatory Authority
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization (Of Technical Requirements for Registration Pharmaceuticals for Human Use)
PPB	Pharmacy and Poisons Board
PD	Product Dossier
PHIS	Pharmaceutical Health Information System
PI	Product Information
SDRA	Stringent Drug Regulatory Authority
SmPC	Summary of Product Characteristics

GLOSSARY OF TERMS

Active pharmaceutical ingredient (API)	An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals. *(USFDA Glossary of terms, it can be found online at Drugs@FDA Glossary of Terms).*
Active Pharmaceutical Ingredient (API) starting material	A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. (*WHO Glossary of Terms*).
Commitment batches	Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.
Comparator product	A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.
Existing API	An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority. (*WHO Glossary of Terms*).
Finished pharmaceutical product (FPP)	A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling. (*WHO Glossary of Terms*).
Generic product	Is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference

	medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. *(PHIS Glossary 2009, can be found online at: http://phis.goeg.at/index.aspx? alias=phisglossary)*
Innovator medicinal product	Generally, the medicinal product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality. (*WHO Glossary of Terms*).
Manufacturer	A manufacturer is a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. It involves operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals. *(PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)*
Market Authorization Holder (MAH)	Is a person resident/domiciled to each of the PPB Partner States who holds authorization to place a medicinal product in the PPB Partner Sates and is responsible for that product.
Mock-up	A copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/ labelling of the medicine. It is also referred to as a *paper copy* or *computer-generated version*.
Officially recognized pharmacopoeia (or compendium)	The official recognized pharmacopoeias in the PPB-MRH project are British Pharmacopoeia (BP), European Pharmacopoeia (Ph Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP).

On-going stability study	The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP. (*WHO Glossary of Terms*).
Pilot-scale batch	A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified. (*WHO Glossary of Terms*).
Primary batch	A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. (*WHO Glossary of Terms*).
Production batch	A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.
Specimen	A sample of the actual printed outer and inner packaging materials and package leaflet.

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GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET, AND LABELLING

Introduction

Background

This guideline provides guidance for applicants preparing to submit Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), and Labelling requirements when submitting the documents during the marketing Authorisation Review.

Scope

These guidelines will assist applicants to prepare SmPC, PIL, and Labelling requirements when submitting products for Market Authorisation.

Language

In terms of this guideline, all applications for SmPC, PIL, and labelling should be presented in English (UK). Original documents not in English should be accompanied by an English translation.

A. FORMAT AND CONTENT OF SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

PRINCIPLES OF PRESENTING INFORMATION

i. The SmPC should be worded in clear and concise language.

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

iii. Consistent medical terminology from the Medical Dictionary for Regulatory Activities (MedDRA) should be used throughout the SmPC.

iv. The SmPC provides information on a particular medicinal product; therefore, it should not include reference to other medicinal products (e.g., through statements such as "Like other medicines of the same class …") except when it is a class warning recommended by a competent authority.

SMPC FORMAT AND CONTENT

The SmPC will be structured and populated as outlined in 1-10 below.

1. NAME OF THE MEDICINAL PRODUCT

Both the strength and the pharmaceutical form should follow the proprietary name. However, when otherwise referring to the medicinal product throughout the SmPC text, the strength and the pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product. The use of pronouns (e.g., "it") is encouraged whenever possible.

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, 750mg. The use of decimal points should be avoided where these can be easily removed (e.g., 250 micrograms, 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 micrograms, 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 abbreviated.

Pharmaceutical form

The pharmaceutical form of a medicinal product should be described by a PPB standard term (see Appendix 1). 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 the proper administration of the medicinal product, should be provided in section 2 of the SmPC and as appropriate in section 4.3 or 4.4. Excipients that are required to be declared on the labelling (see *PPB Guidelines on Format and Content of Labels for Medicinal Products*) should be stated here under a separate subheading qualitatively, and, quantitatively. The following standard statement should be included at the end of the section, i.e. 'for a 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

The active substance should be declared by its recommended INN accompanied by its salt or hydrate form if applicable. References to the pharmacopoeial quality should not be included.

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 recognised standard terms which could be complemented with another term if more meaningful to healthcare professionals.

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 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 terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed *in situ.*

Esters and pro-drugs

If the active substance is an ester or pro-drug, the quantitative composition should be stated in terms of the quantity of the ester or pro-drug. When the active 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).

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.

Parenterals excluding powders for reconstitution

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

For multi-dose and large volume parenterals, the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml, etc. as

appropriate, except for multidose vaccines containing 'n' doses of the same dose. In this case, the strength should be expressed per dose volume. Overages or overfill should not be included.

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

Powders for reconstitution prior to parenteral administration

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

Concentrates

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

Transdermal patches

The following quantitative details should be given: the content of active substance(s) per patch, the mean dose delivered per unit time, and the area of the releasing surface, e.g. 'Each patch contains 750micrograms of estradiol in a patch size of 10 cm2, releasing a nominal 25 micrograms of estradiol per24 hours'.

Multidose solid or semi-solid products

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

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 <by recombinant DNA technology>". 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 <animal>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 the 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.

Herbal medicinal products

The quantitative declaration should be in accordance with the existing quality guidelines on herbal medicinal products.

3. PHARMACEUTICAL FORM

The pharmaceutical form should be described by a full standard term of the PPB using the singular form. The term used in this section should be the same as the term used in section 1. 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. In the 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.

Information on pH and osmolality should be provided, as appropriate. In the case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. The appearance of the product after reconstitution should be stated in sections 4.2and 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Study endpoints should not normally be included. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

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

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

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

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

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

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/m^2) should be specified per dose interval for each category where appropriate (specify age/weight/body surface area of subsets of the population as appropriate). The frequency of dosing should be expressed using time units (e.g., once or twice daily or every 6 hours) 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 the 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 antiemetic's) with cross-reference to section 4.4,

- The intake of the product in relation to drinking 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 treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose titration.

Where relevant to the particular product, the following should appear 'The potency of this medicinal product is expressed in <proprietary name> units. These units are not interchangeable with the units used to express the potency of other <active substance name> 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 for any subsets of the elderly population, with cross-reference to other sections providing information on the 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 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 populations (e.g., patients with other concomitant diseases 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/m^2) 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 for preterm and new born should be presented taking into account the more appropriate age e.g., gestational age or 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 the 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 paediatric 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 methods 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 paediatric 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 x to y<months, years><*or any other relevant subsets e.g., weight, pubertal age, gender*><has><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 to y<years, months><*or any other relevant subsets e.g., weight, pubertal 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 <the paediatric 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 (<*Precaution to be taken before manipulating or administering the product*>), 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 section6.6 'Special precautions for the disposal of a used medicinal product and another handling of the product' (or in section 12 if appropriate) and cross-referenced here.

When supportive data are available, information on the alternative method(s) to facilitate administration or acceptability should be given as

explicitly as possible (e.g., the possibility of crushing the tablet, cutting tablet or transdermal patch, pulverizing 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 <bad taste>,
– "the enteric-coated tablet should not be crushed because coating prevents <pH sensitive degradation><irritant effects> 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 new-borns in whom quite often fluids have to be restricted - it would be useful to have information on the maximal concentration that can be safely administered (e.g., "*no more than X mg of Y/ml of the 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 program 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 a 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 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.

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

Lack of data alone should not lead to 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 subheading.

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 the use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not 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 minimization 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", and "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 anaesthetic or patients with cardiac failure. 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 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. Recommendations 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 are 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 are necessary with respect to transmissible agents.
- Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamics 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., the 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 breastfeeding, the ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and4.5, 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 sections 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 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 is not recommended (cross-refer to section 4.4), and

- Precautions include dose adjustment (cross-refer to sections 4.2 or 4.4, as appropriate), mentioning specific situations where these may be required.

b) Any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters.

c) A 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 were in vitro results on inhibition or induction potential should be summarized.

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

This section should mention the duration of interaction when a medicinal product with clinically important interaction (e.g., enzyme inhibitor or inducer) is discontinued. Adjustment of dosing may be required as a result. The implication of 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 purposes, should also be given. With regard to pharmacodynamics 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 areas 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 interaction is more severe or the magnitude of 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 metabolizing enzymes or certain genotypes, this should be stated.

Paediatric 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 pharmacodynamics and 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).

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 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 a pregnancy test or contraceptive measures. Where 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 foetus, 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:

- Recommendations on the use of the medicinal product during the different periods of gestation, including the reason(s) for these recommendations, should be given.
- Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as foetal ultrasound, and specific biological or clinical surveillance of the foetus or the neonate) should be given.

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

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 adverse reactions in nursing neonates should be included if available.

Conclusions from non-clinical studies on the transfer of the active substance and/or its metabolite(s) into milk should be given 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.

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 pharmacodynamics and pharmacokinetics 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) a 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).

4.8 Undesirable effects

This section should include all adverse reactions from clinical trials, post-authorization safety studies, and spontaneous reporting for which, after a 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 authorization 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.

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. Paediatric 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 treatment, it may be important to inform about non-serious adverse reactions that are frequent at the beginning of the treatment but may disappear with its continuation. Another example would be to inform about adverse reactions 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). The 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., 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-authorization 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 reaction 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 the 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, and 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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); 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 to 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 reactions, which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice.

This section should include information characterizing individuals' seriously 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 cross-referenced 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. Paediatric population

A paediatric 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 <expected> 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 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 <1/10) or very common (≥1/10), the frequencies should be provided in parentheses.

In case of major differences with the safety profile in adults, a summary of the safety profile in children could be presented to facilitate the presentation of the information. Available information, from any source, scientifically validated, on 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 the 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 the frequency of adverse reactions

The estimation of the frequency of an adverse reaction depends on the data source (i.e., clinical trial, post-authorization 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 the 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 as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, reactions that represent a syndrome complex should ordinarily be grouped 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 another 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 categories. 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 particularly 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 the 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

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 for 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 is specifically observed in special populations such as the 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

5.1 Pharmacodynamic properties

Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber and other healthcare 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 3rdlevel (pharmacological subgroup) and the 4th level (chemical subgroup) is recommended. If an ATC code is not yet available, this should be mentioned as 'not yet assigned.

In the case of a medicinal product Authorized as a similar biological medicinal product, the following statement will be included:

<<(Proprietary) Name> is a biosimilar medicinal product.

- 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 endpoints 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 the effects should be described using absolute figures. (Relative risks or odd ratios should not be presented without absolute figures).

In 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.

Paediatric population

The results of all pharmacodynamic (clinically relevant) or efficacy studies conducted on children should be presented under this subheading.

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 the results of studies, particular attention should be given to including 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 patients), 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.

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 an 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.

Absorption: complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; T_{max}; the influence of food; in case of locally applied medicinal product the systemic bioavailability; involvement of transport proteins. If available, information on the site of absorption in the gastrointestinal tract should be stated (as it may be important for administration by enteral feeding tubes).

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

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.

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.

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. 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, and hepatic disease, including the 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/pharmacodynamics relationship(s)

- Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint, or side effect).
- The population studied should be described.

Paediatric population

Results of pharmacokinetic studies in the different paediatric age groups should be summarized, with a comparison to adults if available. If appropriate, the dose producing similar product exposure as indults 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 recognizing the safety profile of the medicinal product used for the authorized 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 more than 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 *Guidelines on format and content of labels for medicinal products*

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 the 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 antibiotics or other antimicrobial agents used in production that are known allergens with the potential for inducing undesirable effects should be mentioned in sections 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 recognized pharmacopoeial name. If an excipient has neither an INN nor a pharmacopeia 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 recognized action or effect).

The ingredients in excipient mixtures should be listed individually. In cases where the full composition of a flavor or fragrance is not known to the applicant or is too complex, it may be declared in general terms (e.g. 'orange flavor', 'citrus perfume'). However, any of the components, which are known to have a recognized 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)'

Proprietary 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. 'pregelatinized 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 recognized 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 labeling, on the 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 the 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

The shelf life should be given for the medicinal product as packaged for sale and, if appropriate, after dilution or reconstitution or after the first opening.
A clear statement of the shelf life should be given, in an appropriate unit of time.

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 paediatric 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 of 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 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.

6.4 Special precautions for storage

Storage warnings should be stated.
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 PIL.

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 the container

Reference should be made to the immediate container using recognized pharmacopeial standard terms; 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 of 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, and 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.

If appropriate, it should be indicated if the container closure is child-resistant.
Examples of the text in this section:

'<Volume> ml suspension in a pre-filled syringe (glass) with a plunger stopper (chlorobutyl rubber) with or without a 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, a number of doses (e.g., multi-dose vaccines, inhalers, etc.), the total weight or volume of the immediate container, as appropriate, and the number of containers present in an 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 <and other handling>

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

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

In section 4.2, instructions on the handling of the product by the doctor, other health personnel, or patient should be included, as well as general information concerning the administration of the product (whether administered by the patient or the health personnel). If instructions for use/handling are needed where the medicinal product has to be prepared before use, e.g. where it must be suspended or diluted, this information has to be given here.
For clarity, a cross-reference in section 4.2 to the relevant information in section 6.6 could be included, e.g. 'For instructions on dilution of the product before administration, see section 6.6.'

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

Information on the preparation (e.g. the suspension of a powder for injection, or preparing a dilution) of the medicinal should be included in

section 6.6, regardless of who prepares the product (e.g. pharmacist, doctor, other health personnel, patient, parents, or carers). In the case of products for reconstitution, the appearance of the product after reconstitution should be stated.

Statements concerning the compatibility of the product with other medicinal products or devices can be given here provide 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 AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Name and permanent address or registered place of business of the Marketing Authorization Holder and manufacturing site(s) physical address.

Telephone, fax numbers, or e-mail addresses may be included (not websites or emails linking to websites).

8. MARKETING AUTHORIZATION NUMBER

Item to be completed by the Marketing Authorization Holder once the Marketing Authorization has been granted by the PPB Partner State

9. DATE OF FIRST <REGISTRATION> / RENEWAL OF THE <REGISTRATION>

Item to be completed by the Marketing Authorization Holder once the Marketing Authorization has been granted or renewed.

Both the date of first authorization and, if the authorization has been renewed, the date of the (last) renewal should be stated in the format given in the following example:

Date of first authorization: 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 Authorization.

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.

B. FORMAT AND CONTENT OF LABELS FOR PHARMACEUTICAL PRODUCTS

1. GENERAL REQUIREMENTS

(a) The label texts

Particulars in the label shall be easily legible, clearly comprehensible, and indelible.

(b) Conformity with the Summary of Product Characteristics

The label text should be in conformity with the summary of product characteristics.

(c) Language

The labelling must be presented at least in English and any other language as may be required by the PPB where the product is placed on the market. If more than one language is used, then all of the text must be in each language and the overall readability should not be adversely affected. The content of all language versions must be identical. It is recommended to group different text elements for each language, where appropriate.

(d) Products with different strengths

Container labels may look similar across multiple strengths of the same product or across multiple products within a company's product line.

Product labels for medicinal products with multiple pharmaceutical strengths, within a manufacturer's product line, should be designed such that the products are identifiable and can be significantly differentiated from one another. Colour differentiation on product labels should be an effective tool that can differentiate products within a manufacturer's product line.

When applying differentiating colour, the applicant should ensure that the text highlighted by the differentiating colour has adequate colour contrast against the background colour on the container label.

(e) Label layout and artwork

Images, pictograms, and other graphics may be used to aid comprehension of the information on the labels of non-prescription medicines only and not on the container labels of prescription medicines.

Images, pictograms, and other graphics should exclude any element of a promotional nature and should only be used to aid navigation, clarify or highlight certain aspects of the text and should not replace the actual text.

The overall layout should not be misleading or have any inappropriate connotations in a way that no doubt about the meaning of a particular pictogram will be perceived.

2. PARTICULARS TO BE INCLUDED ON THE LABEL

(a) Outer packaging or, where there is no outer packaging, on the immediate packaging

The label should include at least the following:

i. Proprietary Name where applicable

ii. International Non-Proprietary name(s) of the Active Pharmaceutical Ingredient(s)

iii. Amount of each Active Pharmaceutical Ingredient present in a dosage unit

iv. List of excipients known to be a safety concern for some patients, e.g., lactose, gluten, metabisulfites, parabens, ethanol, or tartrazine. For parenteral and topical preparations, all excipients should be listed.

v. Pharmaceutical form and contents of the container, e.g., number of dosage units, weight, or volume.

vi. Method and route(s) of administration and the statement “Read the patient information leaflet before use.”

vii. Special warning that the medicinal product must be stored out of the reach and sight of children ("Keep out of the reach and sight of children").

viii. Other special warnings and handling precautions, if necessary (e.g., in case of specific toxicity of the agents)

ix. The word "sterile" if the product is sterile

x. A batch number assigned by the manufacturer

xi. The manufacturing date

xii. The expiry date

xiii. Special storage conditions, if applicable

xiv. Special precautions for the disposal of unused medicinal products or waste material derived from such medicinal products, if appropriate

xv. The name and address of the Marketing Authorization Holder in the PPB

xvi. The physical address of the site responsible for the release of the finished product

xvii. Advice on general classification for distribution, e.g., Controlled Medicines, Prescription Only Medicines, Pharmacy Only Medicines, Over-the-Counter, and General Sales List

xviii. Instruction on use

xix. The proprietary name, strength, and expiry date in braille (Marburg Medium)

xx. A unique identifier (for example a product-specific barcode, unique code, or registration number issued by PPB).

(b) Guidance for small containers

For containers of less than or equal to 10 ml capacity that is marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container should contain at least this minimum information (added):

i. Brand Name of the FPP, INN name, strength, pharmaceutical form, active substance(s), and route(s) of administration.

ii. Method of administration

iii. A batch number assigned by the manufacturer
iv. Expiry date
v. Manufacturing date if space is enough
vi. Contents by weight, by volume, or by unit
vii. The name and address of the manufacturing site— or a logo that unambiguously identifies the company.
viii. Directions for use, and any warnings or precautions that may be necessary

(c) Guidance for Blisters and strips

Blisters and strips should include, as a minimum, the following information (printed directly): -

i. Name, strength, and pharmaceutical form of the FPP.
ii. Name and physical address of the manufacturing site (the site responsible for the release of the finished product)
iii. The batch number assigned by the manufacturer
iv. The expiry date [Note that for co-blistered products, the expiry date is that of the product which expires first.]
v. The manufacturing date, if space is enough
vi. The batch number assigned by the manufacturer
vii. Directions for use, and any warnings or precautions that may be necessary.

(d) Additional labelling information is required by some Partner States

Partner State PPBs may require the use of certain forms of labelling making it possible to indicate:

i. Price of the medicinal product;
ii. The reimbursement conditions of social security organisations;
iii. Identification and authenticity;
iv. A statement that the product is a property of the government

The information specific to a Partner State PPB should be accommodated on the label in a box, to appear on one side of the pack.

Each box should only be presented in the official language or languages of the Partner State concerned and should state the name of that Partner State.

3. CONTROL OF THE CONFORMITY OF THE LABELLING

The labelling of the medicinal product forms part of the authorization and it must, therefore, be approved by PPB when the authorization is granted.

4. CHANGES TO THE LABELLING

Any changes to the labelling, which are not connected with the Summary of Product Characteristics, shall be notified to the PPB where authorization is granted. Therefore, if a Marketing Authorization Holder wishes either to introduce any label text additional to that in the decision or to change any aspect of the labelling he must first notify this change to the relevant mentioned, who shall inform the Marketing Authorization Holder whether the proposed change is accepted or not.

C. FORMAT AND CONTENT OF PACKAGE INSERTS FOR PHARMACEUTICAL PRODUCTS

1. GENERAL REQUIREMENTS

1.1 The Package Insert

Particulars in the package insert shall be easily legible, clearly comprehensible, and indelible.

a) Type size and font

The following should be considered while selecting type size and font:

i. The font should be easy to read; stylized fonts which are difficult to read should not be used;

ii. The font should be such that similar letters/numbers such as “I”, “l” and “1” can be easily distinguished from each other;

iii. A minimum type size of 9 points, as measured in font 'Times New Roman, not narrowed, with a space between lines of at least 3 mm, should be used;

iv. Widespread use of capitals is discouraged; however, capitals may be used for emphasis.

b) Paper

The quality of the insert paper should be taken into consideration in order to ensure proper readability of the insert. The following should be considered:

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

ii. Uncoated paper is preferred as glossy paper reflects light thus making information difficult to read.

iii. When the leaflet is folded the creases should not interfere with the readability of the information or lead to the tearing of the insert.

1.2 Conformity with the Summary of Product Characteristics

The package insert should be in conformity with the summary of product characteristics.

1.3 Language

The labelling must be presented at least in English. An active style of writing should be used instead of passive.

2. PARTICULARS TO BE INCLUDED ON THE PACKAGE INSERT

2.1 Content and format of the prescribing information

For prescription-only medicines, the package insert should include prescribing information. The content and format for the prescribing information should follow that of Summary of Product Characteristics (SmPC). Please refer to the *PHARMACY AND POISONS BOARD*

Guidelines on Format and Content of Summary of Product Characteristics for Pharmaceutical Products.

2.2 Content and format of the patient information leaflet

The patient information leaflet shall include the particulars outlined in the template in the following section.

The applicant should complete the template and delete the parts which are not applicable.

2.2.1 Template for a patient information leaflet

{(Proprietary) name strength pharmaceutical form}

{Active substance(s)}

Read all of this leaflet carefully before you start <taking><using> this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your <doctor, health care provider><or><pharmacist>.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor, health care provider><or><pharmacist>.>

In this leaflet:

a) What {product name} is and what it is used for
b) Before you <take><use> {product name}
c) How to <take><use> {product name}
d) Possible side effects
e) How to store {product name}
f) Further information

[Delete sections that are not applicable]

a) WHAT {PRODUCT NAME} IS AND WHAT IT IS USED FOR

b) BEFORE YOU <TAKE><USE> {PRODUCT NAME}

Do not <take><use> {product name}

– <if you are allergic (hypersensitive) to {active substance(s)} or any of the other ingredients of {product name}.>
– <if ...>

Take special care with {product name}

– <if you ...>
– <when ...>
– <Before treatment with {product name},...>

<Taking><Using> other medicines

<Please tell your <doctor, health care provider><or><pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>

<Taking><Using> {product name} with food and drink

Pregnancy and breast-feeding

<Ask your <doctor, health care provider><or><pharmacist> for advice before taking any medicine.>

Driving and using machines

<Do not drive <because...>.>

<Do not use any tools or machines.>

Important information about some of the ingredients of {product name}

c) HOW TO <TAKE><USE> {PRODUCT NAME}

<Always <take><use> {product name} exactly as your doctor or health care provider has told you. You should check with your <doctor, health care provider><or><pharmacist> if you are not sure.><The usual dose is…>

<Use in children>

If you <take><use> more {product name} than you should

If you forget to <take><use> {product name}

<Do not take a double dose to make up for a forgotten <tablet><dose><…>.>

If you stop <taking><using> {product name}

<If you have any further questions on the use of this product, ask your <doctor, health care provider><or><pharmacist>.>

d) POSSIBLE SIDE EFFECTS

Like all medicines, {product name} can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor, health care provider><or><pharmacist>.

e) HOW TO STORE {PRODUCT NAME}

Keep out of the reach and sight of children.

<Do not store above ºC>, <Store in the original <container><carton>>

Do not use {product name} after the expiry date which is stated on the <label><carton><bottle><…><after {abbreviation used for expiry date}.><The expiry date refers to the last day of that month.>

<Do not use {product name} if you notice {description of the visible signs of deterioration}.

<Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.>

f) FURTHER INFORMATION

What {product name} contains

- The active substance(s) is (are)…
- The other ingredient(s) is (are)…

What {product name} looks like and what contents of the pack

Name and full physical address of Marketing Authorization Holder and Manufacturing site:-

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

For any information about this medicinal product, please contact the <local representative of the> supplier:

{Country}	**{Country}**
{Name}	{Name}
<{Address}	<{Address}
B-0000 {City}>	B-0000 {City}>
tel: + {telephone number}	tel: + {telephone number}
<{e-mail}>	<{e-mail}>

<as appropriate, add additional local representatives to the above table>

This leaflet was last approved in {MM/YYYY

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