SADC MRH PROJECT

GUIDELINE ON PRODUCT INFORMATION AND LABELLING

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2 INTRODUCTION

Southern African Development Community (SADC), as a region has harmonized medicinal products registration guidelines in the common technical document (CTD) format that were approved in January 2015. Nevertheless, the harmonization of product information and labelling requirements within the region has been outstanding. Harmonizing regulatory standards to create one regional market and mutual recognition is one of the strategies included in the draft Strategy on Regional Manufacturing of Essential Medicines and Health Commodities (2016-2020), which supports the pharmaceutical component in the SADC Industrialization Strategy and Roadmap 2015 – 2063. Moreover, this supports the priority areas of creating an enabling regulatory environment and strengthening medicinal products regulatory capacity in the approved SADC Pharmaceutical Business Plan 2015 – 2019.

Taking into account the need for stakeholder engagement in drafting regulatory guidelines, a workshop with industry and regulators was held in Johannesburg, South Africa in April 2016 as the initial step in developing a regional guideline on product information and labelling. This engagement resulted in drafting instructions for the product information and labelling guideline that were approved by the regulators forum. Subsequently, these drafting instructions were utilized for formulating the guidelines presented in this document.

The objectives of this guideline are to:

(i) Define the minimum product information requirements for products intended for the SADC market. Product information includes the Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Product Label;

(ii) Enable applicants/marketing authorisation holders to ensure that all product information is of high quality when submitted to SADC member states as part of applications for new marketing authorisations or updates to existing marketing authorisation;

(iii) Enable applicants/marketing authorisation holders to ensure that the critical product information necessary for the safe use of the medicinal product is included;

(iv) Enable applicants/marketing authorisation holders to ensure that all product information is legible, easily accessible and that users of the products are assisted in assimilating this information so that confusion and error are minimized.

3 SCOPE

This guideline represents the current thinking on this subject. It does not create or confer any rights for or on any person and does not operate to bind the SADC medicine regulatory authorities or the public. The guidance has been drafted to support the legal framework set out in the national legislation in member states. An alternative approach may therefore be used if such approach satisfies the requirements of the applicable statutes and regulations in the member states. The guidelines will apply in all SADC member states namely Angola, Botswana, Comoros, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia and Zimbabwe. It is the applicant's/marketing authorisation holder's responsibility to ensure that the product information complies with all the relevant requirements for the application.

These guidelines apply to both generic (multisource) and new medicinal products (innovator). They also have equal applicability to medicinal products that require a prescription, those available over the counter and general sale medicines. The guidelines have primarily been developed to apply to medicinal products for human use; they however may be used for veterinary medicinal products depending on the country context. It is acknowledged that when used for veterinary medicinal products certain aspects of the guideline would require reviewing and alignment. The product information for complimentary medicinal products is however outside the scope of this guideline.

4 GLOSSARY

Active Pharmaceutical Ingredient (API) /Active Substance/Drug Substance/Medicinal Substance
A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound.

Adverse Drug Reaction (ADR)
A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function.

Applicant/Market Authorisation Holder
The person or company that applies for registration or marketing authorisation of a new pharmaceutical product or an update or variation to an existing marketing authorisation.

Batch (or lot)
A defined quantity of starting material, packaging material or bulk, intermediate or finished product that is intended or purported to be homogeneous in character and quality, and which has been produced during a defined cycle of manufacture.

Biological
A medicinal product that contains one or more active substances made by or derived from a biological source. In the broadest sense, biological medicinal products include any substance made in the laboratory from a living organism.

Biosimilar
A medicinal product which is similar to a biological medicinal product that has already been authorised (the 'biological reference medicinal product'). The active substance of a biosimilar medicinal product is similar to the one of the biological reference medicinal product.

Business Address
It is used interchangeably with physical address to describe a place or location where a given activity such as manufacturing is carried out.

Carcinogenic
A substance which is capable of causing uncontrollable/malignant proliferation of cells in animal or human body.

Category for Distribution/Scheduling Status
Listing or placing of medicinal products in different groups in accordance with approved level of control when being dispensed.

Clinical Trial
A systematic study on pharmaceutical products in human subjects in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism, and excretion of one or more investigational medicinal products with the objective of ascertaining their efficacy and safety.

Common Name/ Generic Name/International Non-proprietary Name
A generic name, publicly owned internationally, that identifies active ingredient(s)/substance(s) or excipient(s) of pharmaceutical product in existence worldwide.

Composition
List of ingredients, and the respective quantitative content of the active ingredient(s).

Consumer
An individual, including his/her family and caregivers, who uses the services of a healthcare provider including a patient receiving medical care or treatment.

Contra-indication
Situation in which the drug should not be used because of the risk of use, which outweighs any possible beneficial effects.

Dosage Form
The form of a pharmaceutical product intended for accurate and convenient delivery of the active ingredient to the site of action e.g. tablets, suppositories.

Expiry Date (Expiration date)
A date placed on the container or label of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specifications, if stored under defined conditions and after which it should not be used.

General Sale Medicine
Any medicinal product whose use does not need the direction or prescription by a healthcare professional.

Generic Products
A pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of the patent or other exclusivity rights.

Indications of the Product/Therapeutic Indication
A description of the disease to be treated with the medicinal product, and the population for which the medicinal product is intended.

Innovator Pharmaceutical Product

A pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of adequate documentation of efficacy, safety and quality (according to requirements at the time of the authorisation).

Interactions
An effect of one substance being changed by the presence of another substance or by some environmental chemical agent.

Labelling
A process of putting information on the immediate or outer package.

Marketing Authorisation
An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It normally contains product particulars, information on which authorisation is based, approved product information` and address and name of the holder of the authorisation, and the period of validity of the authorisation.

Medicinal Product
Any preparation for human use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Medicine Interactions
An act of two or more medicinal products affecting each other either pharmacodynamically or pharmacokinetically or both.

Patient Information Leaflet (PIL)
A leaflet containing information for the patient regarding of the product in language that is understandable to the patient/caregiver.

Pharmaceutical Dosage Form
A pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution) suitable for administration to human subjects.

Pharmaceutical Product
Any preparation for human use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Pharmacodynamic Properties
Biochemical and physiological effects of medicinal products and the mechanisms or mode by which they are brought about.

Pharmacokinetic Properties
The processes of bodily absorption, distribution, metabolism and excretion of medicinal products.

Precaution(s) for Use
Special care to be exercised by prescriber and patient in the handling and use of a medicinal product.

Precaution(s) for Storage
Special care to be taken into consideration to prevent contamination and deterioration of a medicinal product in relation to the effects of atmosphere, moisture, heat and light.

Product Information
A document defining information that may be supplied with or about a pharmaceutical product by or on behalf of the marketing authorisation holder. This would include the Summary of product characteristics (SmPC), Patient information leaflet (PIL) and Product label.

Product Label
All information that appears on any part of a container, including that on any inner/immediate/primary label and outer/secondary label of the packaging.

Proprietary Name
A commercial name granted by a naming authority for use in marketing a product in a particular jurisdiction.

Registration Number
A number assigned to a medicinal product after being granted marketing authorisation.

Registration Status
Means either of 'registered', 'pending', 'rejected', 'withdrawn', 'suspended, 'revoked' 'cancelled' or 'refused'.

Route of Administration
The site or area where a medicinal product is introduced into the human or animal body from where it is absorbed and or transported to its site of action; such as; oral, intravenous, intramuscular, subcutaneous, intravaginal, rectal, intradermal, topical, etc.

SADC Member States
Includes Angola, Botswana, Comoros, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia and Zimbabwe.

Shelf Life
The time interval during which a product is expected to remain within the approved shelf-life specifications, provided that it is stored under the conditions defined on the label in the proposed container closure system.

Special Warnings

A statement that informs in advance about a possible danger or unpleasant condition that is likely to happen when using a medicinal product.

Side Effect
Unintended effect occurring at normal dose(s) related to the pharmacological properties of the medicinal product.

Storage Conditions
An acceptable variation in temperature, light and relative humidity under which an API or medicinal product may be stored for the duration of the shelf life while retaining its characteristics.

Strength
Strength of the medicinal product means the content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or mass or weight according to the dosage form.

Summary of Product Characteristics (SmPC)/Package Insert (PI)/Professional Information (PI)
The SmPC is a legal document approved as part of the marketing authorisation of each medicinal product. It is the basis of information for healthcare professionals on the medicinal product.

Teratogenic
Causes harm to the developing embryo.

Toxicology
Science of substances as causes of adverse or undesired effects and diseases in man, including sources, appearance, chemical composition, properties, biological actions, detection and method of treatment (antidotes).

5 PRODUCT INFORMATION

The product information is important for safe use of the product by the healthcare professionals as well as the patients or users. It is also important for detecting substandard and falsified (SF) medical products. Product information is part of the regulatory notification or approval decision for a product, legally binding and is the responsibility of the applicant/ marketing authorisation holder.

Product information needs to be regularly reviewed and where necessary updated. Any product information changes require regulatory approval. In principle, product information for the innovator product is based on the scientific efficacy and safety data while that for a generic product is based on the copy of the reference/innovator product.

A tripartite approach of (i) the summary of product characteristics (SmPC), intended for healthcare professionals, (ii) patient information leaflet (PIL) intended for the patient or user and (iii) product labelling has been adopted.

Font sizes for text and tables for the SmPC and PIL should be of a style and size that are large enough to be easily legible even after printing. A type size of 9 points as measured in font 'Times New Roman' not narrowed with at least 3mm space between lines should be considered as a minimum.

The particulars appearing on the label of all medicinal products should be printed in characters of at least 7 points (or of a size where the lower case "x" is at least 1.4 mm in height), leaving a space between lines of at least 3 mm. This is also considered as a minimum requirement for the label.

6 DISSEMINATION AND ACCESSIBILITY OF PRODUCT INFORMATION

Adequate dissemination and subsequent accessibility of product information plays a critical role in the rational use of medicinal products.

The options for the distribution and subsequent accessibility of product information include:

- With the product
- Online access
- Mobile application
- Compilation /book
- Disseminated separately

The regulatory authority in the SADC members state where the product is to be marketed should approve these options for the distribution of the product information.

6.1 Accessibility of the SmPC

- All the options suggested above for the dissemination and subsequent accessibility are a possibility for the SmPC.
- The responsibility of updating the information in the SmPC in any of the distribution options would be that of the applicant/market authorisation holder.
- The applicant/market authorisation holder should ensure that the SmPC of the medicinal product is disseminated and therefore accessible to the healthcare professional in at least two (2) of the five (5) possible mechanisms.
- One of the two options selected by the applicant/market authorisation holder should be with the product. This is in order to enable that all the healthcare professionals in the SADC region can access the SmPC. Having more than one option to access the SmPC is required because there is a wide spectrum of working conditions for healthcare professionals in the region. There are those healthcare professionals that would not have access to online information and thus would require paper-based information and on the other hand, it is recognized that even if the SmPC is included in the package it may not reach the prescriber as the product is usually with the dispenser.
- Over the counter medicinal products may be exempted from supplying the SmPC with the product.
- Bulk medicinal products should have at least one SmPC supplied with the product.
- A single SmPC for different strengths and pharmaceutical forms may be used as long as any information that is specific to a particular strength and/or pharmaceutical form is clearly provided.

6.2 Accessibility of the PIL:

- The PIL should be included within each package of the product and the same version should be available online. Additional methods of dissemination of the PIL may be considered if the applicant/marketing authorisation holder so wishes.
- In principle, a separate PIL for each pharmaceutical form and each strength is required.

6.3 Further Guidance on Product Information Accessibility:

- "Mock-ups"/"specimen" of the product information have to be submitted to regulatory body
- Upon request of patient organisations, product information for visually impaired patients should be provided (e.g. increase in font size of up to 20 points or for the blind a format that is perceptible by hearing).
- Online accessibility of the product information can also be facilitated by the inclusion of a matrix barcode on the product label. The application for reading the matrix barcode should be easily accessible and be supported by mobile devices such as smartphones or tablets.

7 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

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

Category for Distribution/Scheduling Status
The proposed category for distribution/scheduling status should reflect those of all proposed markets in the region as per SADC member state legislation pending regional harmonization.

1. **Name of the medicinal product:**

- This should be the proprietary name of the product as approved by the regulatory authority. The name should include the strength and pharmaceutical form as applied for, e.g. "Artelum 20 mg/120 mg tablets".
- While it is preferable that the chosen proprietary (brand) name be harmonized for the region for ease of identification and regional uniformity, applicants/market authorisation holders may implement relevant market differentiating branding strategies for individual markets in member states.
- In assessing the merits of a proposed proprietary name, the first and overriding consideration is that of patient safety. The proposed proprietary name should be unique and not be liable to result in any confusion in print, handwriting or speech with the proprietary name of another medicinal product.
- The SADC Regional Harmonization Initiative (Zazibona) subscribes to the WHO guidelines regarding the protection of INN stems and encourages the pharmaceutical industry to be continually aware of this issue. In line with the WHO policy on the protection of INN stems, as outlined in a World Health Assembly resolution (World Health Assembly Resolution WHA46.19), proprietary names should not be derived from international non-proprietary names (INNs) and INN stems not be used in such names. Furthermore, the name of the medicinal product should not be liable to confusion with the approved INN name of the API(s).

2. **Qualitative and quantitative composition:**

- Salts or hydrates should be mentioned in terms of the mass approved or INN name of the active moiety, e.g. "Contains 67.5 milligrams of amodiaquine as hydrochloride ".
- Medicinal products intended for oral administration should indicate whether or not they contain sugar or a sweetener, e.g. "contains sugar" or" sugar free or contains sweetener", whichever is applicable. Where there is a sugar known to produce intolerance or side effects, the presence of this sugar should be stated, e.g. "Contains lactose monohydrate".

- Given that pharmacological classifications are different among member states, applicants/ market authorisation holders should include both ATC codes and pharmacological classifications for all proposed markets in the region, pending regional harmonization.
- Further details on the excipients to be declared may be found in the *SADC GUIDELINE ON EXCIPIENTS IN THE LABELLING, SUMMARY OF PRODUCT CHARACTERISTICS AND PATIENT INFORMATION LEAFLET OF MEDICINAL PRODUCTS FOR HUMAN USE*
- Biological medicinal products
    - **Expression of strength:** The quantity of biological medicinal products should be expressed in terms of mass units, units of biological activity, or International units as appropriate for the particular product, and reflecting. compendia usage where relevant. For Pegylated Proteins, relevant guidance should be consulted.
    - **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 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 that is available should be consulted

3. <u>Pharmaceutical form:</u>

- Applicants/market authorisation holders should state pharmaceutical forms
- A visual description of the appearance of the product should be provided. This should include shape, dimensions, colour, marking
- If a score line is present, unless specific quality tests of uniformity of content and weight were confirmed on tablets halved along the score line, a statement on divisibility should be provided, e.g. "The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses."

4. Clinical particulars:

Product information for generic products/biosimilars should not deviate from the innovator's clinical particulars unless they have included scientific data to support the claim(s).The applicant/market authorisation holders should ensure that the posology and method of administration in the SmPC is in line with the dosage form and strength(s) as applied for, including the ability to titrate where required and use in special populations if recommended
In some member states, consideration may be given to treatment guidelines e.g. national treatment guidelines, WHO treatment guidelines

4.1 Therapeutic indications:

- Applicants/market authorisation holders should clearly and concisely define the proposed target disease and population for the medicinal product as applied for; distinguishing between treatment (symptomatic, palliative, 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. e.g., "{product name} is indicated for the treatment of uncomplicated malaria due to artesunate-sensitive strains of *Plasmodium falciparum* in patients weighing 5 kg or more." There should be a clear distinction between treatment, primary prevention, secondary prevention and diagnostic indications.
- For antimicrobials, indications should be linked to conditions caused by organisms for which susceptibility to the medicinal product has been shown, where this information is available.
- It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'invented/product name is indicated in
    - <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.
- Specify if product is exclusively for paediatric use.
- If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication

4.2 Posology and method of administration:

- In case of restricted medical prescription start this section by specifying the conditions.
    - Method of administration: directions for proper use by healthcare professionals or by the patient.
    - Practical details for the patient can be included in the package information leaflet, e.g. in the case of inhalers, subcutaneous self-injection. Instructions for preparation are to be placed under '*Special precautions for disposal of used products/waste material + other handling'*.
- In case of specific safety need, any recommended restriction to a particular setting should also be stated (e.g. "appropriate resuscitation equipment should be available").

- Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).
- For each route of administration and indication include:
    - Dose and dose interval
    - The intake of the medicinal product in relation to fluid and food intake, a cross reference to '*Interaction with other medicinal products and other forms of interaction'* should be included in cases of specific interaction e.g. with alcohol, grapefruit or milk.
    - Duration of treatment where relevant; in particular, if short-term treatment is part of the indication, the duration of treatment should be included as part of the dosage
    - Dosage recommendations for different weight bands or body surface area where appropriate
    - **Special populations:** Dosage adjustments or other posology related information in specific patient groups should be stated where necessary, in well-defined sub-sections ordered by importance, e.g. regarding:

      - Elderly population: it should be made clear whether or not any dosage adjustment is necessary in any subsets of the elderly population, with cross-reference to other sections providing information in elderly.

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

      - Hepatic impairment: specified according to the patients included in studies, for instance compensated or decompensated cirrhosis and the definitions used in the studies, such as Child-Pugh score/grade of the patient.

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

      - Other relevant special population (e.g. patients with other concomitant disease or overweight patients).
    - **Paediatric Population:** The specific sub-section 'paediatric population' should always be included and the information given should cover all subsets of the paediatric population

      - 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 in

preterm newborns should be presented taking into account the more appropriate age e.g. gestational age.

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

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

- Where a product is indicated in children and no adequate paediatric formulation can be developed, detailed instructions on how to obtain an extemporaneous preparation shall be included in '*Special precautions for disposal of used products/waste material + other handling'* with a cross-reference in '*Posology and method of administration'*.

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

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

a) 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 <'*Undesirable Effects'*><'*Pharmacodynamic Properties'*><'*Pharmacokinetic Properties'*> but no recommendation on a posology can be made >

b) 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. 'Undesirable Effects' or 'Pharmacodynamic Properties') >.

c) 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)>.

d) 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 Contraindications).

- Monitoring advice, where applicable

- The following points should be addressed, where appropriate:
  - The maximum recommended single, daily and/or total dose
  - The need for dose titration
  - If relevant, the need for tapering off

- The normal duration of use and any restrictions on duration
- The intake of the medicinal product in relation to food intake
- If necessary, relevant instructions for correct administration/use, including the use of devices
- Where relevant, instructions on how to prepare or reconstitute the medicinal product[s] should be placed in '*Special precautions for disposal of used medicinal products/waste material + other handling'* and cross-referenced here.
- For medicinal products to be reconstituted, the storage condition and shelf life for reconstituted solutions or suspensions should be included in '*Shelf life'*.
- For parenteral preparations: Include information on compatible and incompatible solutions where this may be necessary for administration purposes in '*Incompatibilities'*.
- For extemporaneous preparation: Detailed instructions for use, e.g. for dispersible or parenteral formulations and instructions for extemporaneous preparation in '*Special precautions for disposal of used products/waste material + other handling'*.
- 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 preventative measures to avoid certain adverse drug reactions (e.g. administration of anti-emetics) with cross-reference to '*Special warnings and precautions for use'*.
- It may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose titration.

- **Method of administration:**
  - Any special precautions related to the manipulation or administration of the product (e.g. cytotoxic products) by healthcare providers (including pregnant healthcare providers), the patient or caregivers should be mentioned here under a specific sub-heading (<Precaution to be taken before manipulating or administering the product>) with cross-reference to '*Special precautions for disposal of used products/waste material + other handling'*.
  - For parenteral preparations: Include information on compatible and incompatible solutions where this may be necessary for administration purposes. Information on the rate or speed of injection or infusion should be provided.
  - For parenteral formulations - in children, especially newborns in whom quite often fluids have to be restricted - it would be useful to have information on maximal concentration that can be safely administered (e.g. *"no more than X mg of Y per mg of solution"*).

- 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 (cross-reference '*Pharmacokinetics Properties'*)".

4.3 Contraindications:

- Absolute contraindications could include particular clinical diagnoses, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicinal product or class of medicinal products).
- Where the use of a medicinal product may be life threatening, cause mortality or serious morbidity.
- Medicinal products or classes of medicinal product of which the concomitant or consecutive use should be contraindicated, based on data or where there are strong theoretical reasons (e.g. on grounds of pharmacokinetic properties, pharmacodynamic properties, or common state of knowledge in medicinal product) for not using the combination. (cross-reference to '*Interactions with other medicinal products and other forms of interaction'*.)
- If a safety issue can be predicted in a patient population (e.g. use of a renally cleared substance with narrow therapeutic margin in renal failure patients), or if patients were excluded from studies as being contraindicated on serious grounds of safety. Do not include: Patient populations not studied in the clinical trial programme, unless the above applies. (cross-reference '*Special warnings and precautions for use'*).
- Pregnancy and lactation, if absolutely contraindicated. (cross-reference to '*Fertility, pregnancy and lactation'*).
- Hypersensitivity to any of the ingredients, including excipients.
- Porphyria, if absolutely contraindicated. (cross-reference to '*Special warnings and precautions for use'*)
- For combination products, the contraindications for APIs must be presented for the combination.
- Lack of data alone should not lead to a contraindication. Where for safety reasons, the product should be contraindicated in a specific population, e.g. paediatric or a subset of the paediatric population, it should appear in this section with a cross-reference to the section giving detailed information on the safety issue. A contraindication in the paediatric population should be listed without a sub-heading.
- Contraindications to be presented in bullet format where relevant.

4.4 Special warnings and precautions for use:

- Specific safety issues, especially those that may be fatal, life threatening or cause serious harm (adverse effects), should be placed in a prominently displayed box and/or in boldface type, e.g. hypersensitivity reactions with abacavir. Such information may be displayed at the top of this section or may be displayed at the beginning of the professional information. The order of warnings and special precautions should be determined by the importance of the safety information. Generally, the more serious safety precautions and warnings should be listed first.
- Relative contraindications should appear first, followed by the other special warnings and precautions.
- Relative contraindications are conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled.
- Special patient groups likely to experience medicinal product or class related adverse reactions under normal conditions of use, e.g.:
    - certain age groups (including newborns, paediatric, adolescents and elderly).
    - patients with renal impairment (include the degree of impairment and dosage use modifications). If creatinine clearance (CrCl) is used to indicate renal impairment in adults, use the following:
        - Severe renal impairment: CrCl< 30 ml/min
        - Moderate renal impairment: CrCl> 30 - 50 ml/min
        - Mild renal impairment: CrCl> 50- 80 ml/min
    - If creatinine clearance is used, use the Cockcroft and Gault formula:

"eCrCl (ml/minutes) = (140 - age) x weight (kg) x 0.85 serum creatinine (micromol/L)"

    - hepatic impairment (include the degree of impairment). use Child-Pugh classification or modification thereof
    - cardiac failure (include the degree of impairment - NY Heart Association classification) or where the incidence or severity of the reaction differs in particular populations.
- Serious adverse reactions to which the prescriber needs to be alerted, the situations in which these may occur and the actions that may be required, e.g. emergency resuscitation, or if there are particular risks associated with starting (e.g. first dose effects) or stopping (e.g. rebound, withdrawal effects) the medicinal product, together with the action required for prevention.
- Any need for awareness of symptoms or signs representing early warning of a serious adverse reaction, and any need for specific clinical laboratory or other monitoring and should address why, when and how the monitoring should be conducted. 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 dose reduction is recommended in such circumstances, this should be included under '*Posology and method of administration'* and cross-referenced in this section.

- Clinically relevant interactions where, in general, the use in combination should be avoided (relative contraindication) cross-reference to *'Interactions with other medicinal products and other forms of interactions'*.
- Any adverse reactions referred to in this section or known to result from conditions mentioned in this section must also be included under *'Undesirable Effects'*.
- Descriptions of special warnings and precautions regarding pregnancy and lactation should be addressed under the heading '*Fertility, pregnancy and lactation'*.
- The information may describe e.g. reversibility or time of onset, mechanism of the reaction if of clinical relevance, and action to be taken if specific reactions occur (if of particular importance) or dose relationship. Any differences between different dosage forms in respect of adverse reactions should be stated.
- Any adverse reactions resulting directly from an interaction should be included and cross-referenced to '*Interactions with other medicinal products and other forms of interactions'*.
- Include adverse reactions which apply to the therapeutic, chemical or pharmacological class, which may not have been observed yet in relation to the medicinal product, but which are generally accepted as being attributable to other compounds in the class. The fact that this is a class attribution should be mentioned.
- Measures to be taken to avoid specific adverse reactions should be mentioned here. This includes reactions referred to under '*Undesirable Effects'*, as well as any other adverse events which may occur.
- Interference with daily activities; Include whether X may be affected with mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.
- In the case of anaesthetic medicinal products or medicinal products used for conscious sedation, the above applies for 24 hours. The patient should not make any legal or contractual decisions or drink alcohol for that period.
- For combination products the contraindications for APIs must be presented for the combination. For co-packed medicinal products the special warning and precautions for use of each of the APIs co-packaged should be presented separately if is to be taken sequentially and for those co-packed medicinal products containing multicomponent fixed drug combination and a mono-component medicinal product to be taken at the same time, the special warnings and precautions for use of the APIs must be presented for the combination of the APIs contained in the co-pack
- Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known
- Any particular risk associated with an incorrect route of administration (e.g. necrosis risk with extravasation of intravenous formulation, or neurological consequences of

intravenous use instead of intramuscular use), should be presented, with advice on management if possible

- Include risk management/minimization measure were relevant.
- If relevant, include whether the medicinal product may lead to a positive test for a prohibited substance in competitive sport activities.
- Any special precaution necessary relating to excipients or residues from the manufacturing process.
- **Paediatric Population:**

  - When the product is indicated in one or more subsets of the paediatric population and there are special 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

- Applicants should include information on potentially clinically relevant interactions based on the pharmacology (pharmacodynamic properties and preferably in vivo pharmacokinetic properties) of the medicinal product, particularly on interactions which result in a recommendation regarding the use of the medicinal product.
- Interactions not studied in vivo but predicted from in vitro studies or deducible from other situations or studies should be described if they could result in a change in the use of the medicinal product, cross- referencing to '*Posology and method of administration'* and/or to *'Special warnings and precautions for use'*.
- The order of presentation should first be contraindicated combinations, followed by those where concomitant use is not recommended, and others.
- Interactions affecting the use of the medicinal product concerned (in the SmPC) should be given first, followed by interactions resulting in clinically relevant changes on the use of other medicinal products.
- Interactions referred to in other sections of the SmPC should be outlined and cross-referenced to the other sections.
- The following information should be given for each clinically relevant interaction:
    - contraindication of concomitant use (cross reference to '*Contraindications')*
    - concomitant use not recommended (cross-reference to '*Special warnings and precautions for use'*)
    - Precautions regarding dose adjustment (cross reference to '*Posology and method of administration'* and to '*Special warnings and precautions for use'*), stating specific situations where these may be required. For the actual dose recommendation, cross-reference [refer] to '*Posology and method of administration'*.

- any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters
- mechanism of interaction, if known
- the period of interaction if discontinuation of a medicinal product requires adjustment of the doses of concomitant (interacting) medicinal products, e.g. if a medicinal product is an enzyme inhibitor or inducer
- the need for a washout period when using medicinal products consecutively.

- Information on other relevant interactions such as with food or pharmacologically active substances not indicated for medical purposes, e.g. Grapefruit Juice, St. John's Wort, etc.
- Results demonstrating an absence of interaction should only be mentioned if this is likely to be major clinical interest to the prescriber.
- Include interactions with laboratory tests and investigations.
- If no interactions studies have been performed, this should be stated.
- For combination products the interactions for individual active pharmaceutical ingredient must be stated and characterised according to severity.
- Additionally, potential medicinal product interactions may differ due to different concomitant medications as well as specific issues related to ethnicity and pharmacogenomics. These should be considered where clinically relevant.
- Where too numerous, a tabular format may be preferable for ease of reference, e.g. antivirals".
- **Paediatric Populations:** Interaction with other medicinal products and other forms of interaction if there is an indication for the particular age group.
- The resulting exposure and clinical consequences of a pharmacokinetic interaction can differ between adults and children, or between older and younger children. Therefore;
    - Any identified treatment recommendations should be given in relation to concomitant use in the paediatric subset(s) (e.g. dose adjustment, extra-monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring),
    - If the interaction studies have been performed in adults, the statement 'Interaction studies have only been performed in adults' should be included.
    - If the extent of an interaction is known to be similar in a paediatric age group to that in adults, this should be stated.
    - If this is not known, this should also be stated.
    - The same applies to pharmacodynamic drug interactions.
- In cases of food interaction leading to a recommendation on co-administration with a meal or specific food, it should be specified whether this is relevant for paediatric use (especially new-borns and infants) whose diet is different (100 % milk in new-borns).

4.6 Fertility, pregnancy and lactation:

- Women of childbearing potential/Contraception in males and females

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

- Pregnancy
  - Information on embryo, foetal and newborn toxicity. Include information on teratogenicity, genotoxicity and inadvertent exposure during pregnancy. Include references to trimester(s) of pregnancy. Facts on human experience and conclusions from preclinical toxicity studies, which are of relevance for the assessment of risks associated with exposure during pregnancy. (cross-reference to '*Contraindications'* as appropriate.) Recommendations on the use of the medicinal product at different times during pregnancy in respect of gestation.
  - Statements such as "where the benefit outweighs the risk" or "at the discretion of the medical practitioner" or "should not be used unless clearly necessary" will not be allowed. [When no information is available, the statement "Safety and/or efficacy has not been established" will be allowed.]
  - Recommendations on the management of [the situation of] an inadvertent exposure, where relevant. Include a risk assessment guide (based on human, animal and pharmacological data).
- Breastfeeding
  - Information on breastfeeding or breast-milk is also applicable to babies receiving own-mother's expressed breast-milk or from breast-milk banks and to any possible effects on the baby. Information on excretion of the active substance and/or its metabolite(s) in milk. (Cross-reference to other sections, as appropriate.)
  - A recommendation as to whether to stop or continue the medicinal product while breast-feeding or, alternatively, whether or not mothers taking or using the medicinal product should breastfeed.
- Fertility:
  - Information regarding male/ female fertility should be given in this section.
  - Information on whether/how male or female fertility is affected:
    - whether permanent, temporary or duration of effects
    - sperm structural damage, motility, sperm count or semen volume
    - contraception issues before resuming procreation activities
    - when it is safe to resume procreation activities

- Information on contraception for females and males if she and/or her partner are on treatment with medicinal product{s)
- known to be teratogenic, or cause embryo or foetal harm.
- This section should also include:
  - Clinical data if available;
  - Relevant conclusions from non-clinical toxicity studies, if available. Further details should be included in section '*Preclinical safety data'*;
  -Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment; and
  -If there are no fertility data at all, then this should be clearly stated.

4.7 Effects on ability to drive and use machines:

- On the basis of the pharmacodynamic profile, reported adverse reactions and/or specific studies on a relevant target population related to driving or using machines, specify whether the medicinal product has - no or negligible influence - minor or moderate influence - major influence on these abilities.
- Effects of the disease itself on these abilities should not be discussed.
- It is not always possible to predict to what extent X may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which X affects them. Particularly serious warnings/special precautions for use should be clearly mentioned
- Include whether the medicinal product may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision

4.8 Undesirable effects:

- This section should provide comprehensive information based on all adverse reactions from clinical trials, post-marketing studies or spontaneous reports attributed to the medicinal product.
- This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to healthcare professionals on the safety profile of the product. In addition, the whole section could be revised at the renewal of the registration, where the safety profile of most products is likely to be well established, and after evaluation of time specified at Periodic Safety Update Reports (PSURs)/ Periodic Benefit-Risk Evaluation Reports (PBRERs)
- Include all adverse reactions if they are at least possibly causally related. Information obtained from clinical trials/studies and from post-marketing data should be presented separately.
- This section should not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements, or statements of general

good tolerability. Statements on lack of proof of causal association are generally not helpful and should only be included if of particular relevance.

- To provide clear and readily-accessed information, the section should be structured according to the following recommendations:
    - A brief, general description will be necessary for most medicinal products, providing an estimate of the overall percentage of treated patients expected to experience adverse reactions. This information must be consistent with the figures presented and must not contain general statements such as "well tolerated", "adverse reactions are normally rare", etc.
    - Classification of adverse reactions should be according to a system organ class (SOC) as in MedDRA [or WHOART for data from both pre-marketing and post-marketing sources.
    - Frequency of Adverse Drug Reactions (ADRs).
    - For clinical trials/studies data: Within each SOC, the adverse reactions should be ranked under CIOMS headings of frequency, most frequent reactions first, using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, <1/100); rare (≥ 1/10 000, < 1/1000); very rare (<1/10 000), including isolated reports.
    - Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness, as determined from clinical studies.
    - For pooled data from clinical trials/studies, the frequency category representing the highest frequency should be used.
    - Tabulation of adverse reactions according to a SOC may also be used. Presentation of ADR information relative to placebo should be presented as absolute percentages (not as placebo subtracted).
    - For data from sources other than clinical trials/studies data: When the frequency of occurrence of adverse events is not available from clinical studies, the terms "frequent" or "less frequent" should be used. The following guide should be applied for frequency information obtained from sources other than clinical trials:
      'more frequent', 'very common' and 'common' ≡ 'frequent' 'single reports' or 'isolated reports', 'uncommon', 'rare', 'very rare' ≡ 'less frequent'.
    - Such frequency information may be sourced from SmPC from other stringent regulatory authorities or may be obtained from recognized reference sources. The term reporting the highest frequency should always be used and all information must be clearly referenced.
    - When no frequency data are available for a specific ADR, the statement "frequency not known" or "frequency unknown" may be added, with justification for the lack of information and providing the reference sources consulted. Note: For a MSM SmPC without its own clinical trial data, ADRs should be categorized according to the frequency classification: 'Frequent' and 'Less frequent'.

For post-marketing data:

- Spontaneous reports: Information relating to individual serious and/or frequently occurring adverse reactions, for which there is no frequency estimation available (e.g. obtained from a spontaneous reporting system) must be included. No frequency categories can be allocated to individual reports from a spontaneous reporting system.

  Post-marketing studies:

- Information from post-marketing studies (e.g. phase IV studies) should be separate from that obtained from pre-marketing clinical trials, with frequency categories according to the CIOMS convention (as for clinical trials/study data), and with the study(ies) clearly identified. Post-marketing data side effects should be reflected as frequency unknown.
- If there are, only a few adverse reactions in total in this section, classification by SOC may be unnecessary.
- In the case of combination medicinal products, where it is known which particular adverse reactions are attributable to which component of the combination, the information should be presented separately. For combination products the side effects must be first presented for the combination, and then separately for each API.
- [The information may describe e.g. reversibility or time of onset, mechanism of the reaction (if of clinical relevance), action to be taken if specific reactions occur (if of particular importance) or dose relationship. Any differences between different dosage forms in respect of adverse reactions should be stated.]
- [Any adverse reactions resulting directly from an interaction should be included and cross-referenced to '*Interaction with other medicinal products and other forms of interaction'*.]
- [Include adverse reactions which apply to the therapeutic, chemical or pharmacological class, which may not have been observed yet in relation to the medicinal product, but which are generally accepted as being attributable to other compounds in the class. The fact that this is a class attribution should be mentioned.]
- [Any adverse reaction which may be related to excipients or residues from the manufacturing process should be included.]
- **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.
- **Other Special Populations:**

- Information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype
- Summary of safety profile: Information about the most serious and/or most frequently occurring adverse reactions, indicate timing when reactions occur

4.9 Overdose:

- Describe acute symptoms and signs and potential sequelae of over dosage. If no information is available, include the statement "In overdose, side effects would potentially be exacerbated/ exaggerated" (cross reference to '*Undesirable effects'*).
- Describe recommended management of overdose e.g. treatment is symptomatic and supportive or in relation to specific agonists/antagonists, antidotes or methods to increase elimination of the medicinal product e.g. dialysis (excluding gastric lavage)
- If applicable, counteractive measures based on genetic factors should be described.
- Special Populations: Information specifically observed in special populations such as elderly, patients with renal impairment, patients with hepatic impairment, other concomitant diseases etc. should be included.
- 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/strengths of a formulation for which ingestion of only one dose unit by children can cause fatal poisoning.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

- Describe mechanism of action (if known), and pharmacodynamic effects, relevant to its clinical efficacy.
- For combination products the mechanism of action (if known) and pharmacodynamic effects of each API must be presented separately.
- For antimicrobials agents - Do not include antimicrobial sensitivity data derived from in vitro testing but include data on [in vitro] inherent resistance. - [Include only in vivo data of organisms which have been shown to be eradicated in clinical trials which can be linked to the indications (See INDICATIONS). When efficacy data are not available, in vitro sensitive organisms can be included. This information should be accompanied by a statement that in vitro sensitivity does not necessarily imply clinical sensitivity.
- **Paediatric Population:** The results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented under this sub-heading

5.2 Pharmacokinetic properties:

- 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.
- Pharmacokinetic properties of the active substance(s) relevant for the recommended dose and for the strength and pharmaceutical formulation marketed should be given. This should generally include reference to absorption, distribution, biotransformation, elimination and linearity/non- linearity, as appropriate for the dosage form of the medicinal product marketed. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.
- Include information on the intake of the medicinal product in relation to food intake (i.e. with or without food).
- Include characteristics in specific patient groups with respect to factors such as age, weight, gender, smoking, polymorphic metabolism and concomitant pathological situations such as renal impairment and hepatic insufficiency, when clinically relevant.
- Information on pharmacokinetic properties and pharmacodynamic properties relationship(s) and the contribution (if any) of metabolite(s) should be included, where relevant.
- Information regarding the paediatric population should be included where available.
- For combination products, the pharmacokinetic properties of each API must be presented separately.

5.3 Preclinical safety data:

- Should be included only when of relevance to the prescriber and may include:
    - Repeated dose toxicity
    - Genotoxicity
    - Carcinogenic potential
    - Reproduction toxicity
    - Safety pharmacology
    - Environmental risk

6. Pharmaceutical particulars:

6.1 List of excipients:

- All excipients (not active substance(s)) in qualitative form by INN or usual common name.
- The ingredients in excipient mixtures should be listed individually. In cases where the full composition of a flavour or fragrance is not known to the applicant/market authorisation holder or is too complex, it may be declared in general terms (e.g. ‘orange flavour’, ‘citrus perfume’). However, any of the components, which are known to have a recognised action or effect, should be included. Ingredients that may or may not be added for the pH adjustment should be followed by the parenthesis ‘(for pH-adjustment)’ pH adjusters

should be listed, even if not present in the final product. The constituents of printing inks used to mark the ingested dosage form should be stated. Refer to the *SADC GUIDELINE ON EXCIPIENTS IN THE LABELLING, SUMMARY OF PRODUCT CHARACTERISTICS AND PATIENT INFORMATION LEAFLET OF MEDICINAL PRODUCTS FOR HUMAN USE.*

6.2 Incompatibilities:

- Physical/chemical incompatibilities, when likely to be mixed/co-administered.
- If such incompatibilities are not present then a general 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 '*Special precautions for disposal of used medicinal products/waste material + other handling'.*

6.3 Shelf life:

- A clear statement in appropriate unit of time should be stated.
- In-use shelf life, if appropriate: with storage conditions after first opening should be stated.
- Shelf life should be supported by experimental data provided in the application for registration; should not be cross-referenced to the data from the comparator product (for generics) i.e. it is product specific.'
- 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".
- For products to be reconstituted, the storage condition and shelf life for reconstituted solutions or suspensions should be stated.
- 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.
- 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:

- Standard statements and information should be consistent between the SmPC, label and PIL. Should include storage temperature.
- Other relevant storage instructions such as "Protect from moisture/light" are to be included as appropriate.

***6.5* Nature and contents of container:**

- The description of the container, the standard and material of construction of immediate container (e.g., colourless Type I glass vials or PVC/Al foil blisters)
- Any other component of product (e.g. desiccant, devices).
- If appropriate, it should be indicated if the container closure is child-resistant.
- All pack sizes should be listed. If appropriate, a standard statement, 'Not all pack sizes may be marketed', should be included, in order to alert healthcare providers to the fact that not all listed pack sizes may be available for prescribing or dispensing.

6.6 Special precautions for disposal of used medicinal products/waste material + other handling

- Information on preparation (reconstitution) and special disposal (e.g. cytotoxics) should be included.
- If relevant, a cross-reference to conclusions on the environmental risk assessment described in '*Preclinical safety data'*, Preclinical safety data, can be included.
- If applicable, e.g. for cytotoxics, the following standard statement should be included, 'Any unused product or waste material should be disposed of in accordance with local requirements.'
- If there are no special uses or handling instructions, the standard statement, 'No special requirements.' should be included.
- Statements concerning compatibility of the product with other medicinal products or devices can be given here provided the data have been provided in the dossier
- Information on risks due to occupational exposure should be included in this section

7. <u>Applicant/Marketing Authorisation Holder Particulars:</u>

- The name and address of the applicant/marketing authorisation holder and manufacturer, if different from the MAH should be included. All the approved manufacturing site(s) should be listed on the SmPC.

8. <u>Marketing Authorisation (Registration) Number:</u>

- All applicable registration numbers should be listed.

9. <u>Date of first authorisation /renewal of the authorisation:</u>

- This is the date of first authorisation in each SADC member state e.g. Zambia: xx June 20xx Zimbabwe: xx September 20xx

10. <u>Date of revision of the text:</u>

- Leave blank for a new submission.

- After approval of the medicinal product, include the date of the most recently revised PI as approved by each SADC member state e.g. South Africa: xx January 20xx Namibia: xx February 20xx

8 PATIENT INFORMATION LEAFLET (PIL)

8.1 Reference documents to be supplied

- Patient Information Leaflets are evaluated in accordance with the information provided in the approved SmPC.
- An application to evaluate a PIL for a registered medicinal product would require that the latest approved SmPC also be submitted.
- For new medicinal product applications, the proposed PIL must be submitted at the same time as the proposed SmPC. In this case, the PIL will be evaluated in conjunction with the proposed SmPC.
- Reference to the SmPC for each statement in the PIL should be included in a broad margin provided on the right-hand side of each page for the purpose of evaluation.
- Reference to the exact page/s in the SmPC should be included.
- No references should, however, be included in the finalised, printed PIL.

8.2 Legibility of the PIL:

8.2.1 Print size and type:

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

8.2.2 Syntax:

- Lengthy sentences (i.e. more than 20 words) should be avoided.
- Where appropriate, bullet points should be used. A group of bullet points should be introduced with a colon and a single full stop should be placed at the end of the group. A list of bullet points should begin with the uncommon and specific case and end with the common or general case, unless this is inappropriate for the medicinal product.
  For example:
  Tell your doctor, pharmacist, nurse or healthcare professional if you suffer from:
  - tuberculosis of the lungs
  - any allergies that affect your lungs
  - any chronic lung conditions.
- A minimum number of words should be used in the bullet points and not more than one sentence for each bullet point.

- Where possible there should be no more than nine items where the bullet points are simple and no more than five when these are complex.
- Abbreviations should be avoided. Pronouns (e.g. 'it') should be used in preference to repeating the name of the medicinal product, provided the context clarifies what the pronoun refers to.

8.3 Format of the pil

8.3.1 Heading*s*

- Headings and sub-headings in the PIL and the order of the headings should be in line with the model template of PIL (see Section 4 under PIL of this document).
- Headings and sub-headings should be made conspicuous.
- More than two levels of headings may impair legibility.

8.3.2 Content

- The information contained in the PIL must be in accordance with the SmPC for the medicinal product
- The text must be phrased so that it is readily intelligible for the patient and address the patient or the caregiver.
- Where a specialised term is used, an explanation should be given.
- Repetition of information can sometimes be avoided by cross-referring to information that is under another heading.
- Information not relevant to the patient should be omitted.

8.3.3 Style

- An active and direct style should be used, by placing the verb at the beginning of the sentence,
  For example:
  'take one (1) tablet' instead of '1 tablet should be taken',
  'you should…' is better than 'it is recommended…'
  'give one (1) medicinal product measureful...' where a medicinal product is clearly indicated for children only
- This principle should be adapted as, for example, in the case of 'If ... then' instructions, such as: 'If you feel ill, tell your doctor or pharmacist'.
- This guidance on style may not be appropriate in all languages, nor for all medicinal products (e.g. those that are not self-administered).
- Pictograms may be used as an additional measure if they make the message clearer to the patient but be without any element of a promotional nature.

8.3.4 Product Ranges

- In some instances, there should be a separate PIL for different pharmaceutical forms (e.g. oral and injectables).

- In the event of a medicinal product falling in two different categories of distribution/scheduling status, a separate PIL should be submitted for each category for distribution/schedule.

8.4 Model PIL

This section contains a model template for developing a Patient Information Leaflet. Applicants/market authorisation holders are requested to follow the format stipulated in this section.

Explanatory Notes

An example of a model leaflet is presented in this Section, containing headings and text, which should be used together with examples of text formulated in consumer-intelligible language. For the purpose of explaining this model leaflet, the following tools are used:

- bold type for the headings.

- normal type for text which is either mandatory or usually relevant and is not a heading.

- possible options which applicants/market authorisation holders should adapt e.g. for the relevant pharmaceutical dosage form, route of administration or population for which the medicinal product is intended (e.g. the mother of a child) are presented with a slash, e.g. take / give / use / are given / receive / administered. Mandatory statement should be adapted to the dosage form.

- text included [in italics] are explanatory notes. When these notes are taken out of the model PIL template, all relevant and mandatory text will remain.

- In this model all of the headings are numbered. However, for certain medicinal products, the headings may not all be relevant. In such instances, the corresponding headings should be omitted.

- Throughout the text, "X" indicates the (proprietary) name of the medicinal product.

- In the case of a complementary medicinal product the following shall be included:
    - *a statement identifying the discipline of the medicinal product; and*
    - *if the medicinal product has not received registration with any regulatory authority the disclaimer "This medicinal product has not been evaluated for safety and efficacy by a regulatory authority. This medicinal product is not intended to diagnose, treat, cure or prevent any disease."*

CATEGORY FOR DISTRIBUTION/SCHEDULING STATUS
[The category for distribution/scheduling status of the medicinal product as it appears in the SmPC]

PROPRIETARY NAME, STRENGTH AND DOSAGE FORM

[The proprietary name of the medicinal product (referred to as X throughout this document) and the active ingredient(s) should be stated here in bold, followed by the strength and pharmaceutical form (i.e. as it appears in the SmPC).
[For medicinal products available only on prescription]

- Read all of this leaflet carefully before you start taking / using / are given X
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- X has been prescribed for you personally and you should not share your medicinal product with other people. It may harm them, even if their symptoms are the same as yours. (may be omitted if the medicinal product is not self-administered*).*

[For medicinal products available without a prescription]

- Read all of this leaflet carefully because it contains important information for you.
- X is available without a doctor's prescription, for you to treat a mild illness. Nevertheless, you still need to use X carefully to get the best results from it.
- Keep this leaflet. You may need to read it again.
- Do not share X with any other person.
- Ask your pharmacist if you need more information or advice.

You must see a doctor if your symptoms worsen or do not improve after (number of) days.

1. WHAT X IS AND WHAT IT IS USED FOR

- *[Full statement of the active substance(s) and excipient(s)]*
- *[The active substance(s) (expressed qualitatively and quantitatively) and the other ingredients (expressed qualitatively) should be identified using their names as given in the SmPC and in the language of the text: e.g.]*
  - The active substance is…
  - The other ingredients are… [These should be listed alphabetically. This should be in lower case, except at the start of a sentence and when it is a registered proprietary name e.g. Colourant®. If a preservative or alcohol (2 % or more) is present, the content of each must be indicated as required for the SmPC].
- *[The pharmacotherapeutic group or type of activity should be stated here using language intelligible to the patient, followed by brief description of the indications for use of the medicinal product].*

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE/USE X

Do not take / use X / You should not be given / administered X:

- If you are hypersensitive (allergic) to (active substance) or any of the other ingredients of X. [Include reference to residues, excipients, etc., if applicable].
- If you have absolute contraindications, Information on absolute contraindications, in accordance with the SmPC, should be provided here in patient-intelligible language. This should include chronic accompanying diseases (e.g. kidney insufficiency, liver insufficiency, diabetes and other metabolic diseases), contraindications due to interactions with other medicinal products, contraindications due to excipients and specified conditions for certain categories of users, e.g.

children or the elderly. Care must be taken to ensure that complex details are not omitted. It is not acceptable to state only the common or major contraindications. Belief that a patient cannot understand a contraindication is not a reason for omitting it.

Warnings and Precautions:

- Tell your doctor or healthcare professional before being given the injection:
- Take special care/Special care should be taken with X
  - if you ...
  - when ...
- *[Information, in patient-understandable language in line with WARNINGS AND SPECIAL PRECAUTIONS in SmPC, on relative contraindications, warnings and appropriate special precautions for use should be provided here. Care must be taken to ensure that complex details are not omitted and that they are expressed in a way that patients can understand. It is not acceptable to include only the more common or major warnings/special precautions.]*

- *[A special precaution should be presented as implying the action a patient should take, rather than as factual information that describes a medical condition. The influence of the medicinal product on the patient's behaviour should be described. A differentiation should be made between the influence on cognitive abilities, reactivity and judgment.]*
  [Example]:
  - If you have asthma (or used to), because X can bring on an attack
  - If you are over 60…
  - If X is given to children…
  - X may make you sleepy

- *[Also describe cases (if any) in which the consumer should only use X after consultation with a medical practitioner. Include (as appropriate and if not mentioned in the previous section) reference to chronic accompanying diseases (renal insufficiency, liver insufficiency diabetes and other metabolic diseases).] [Where applicable, provide information on necessary examinations, which may be carried out by the medical practitioner prior to, or during, the therapy, for example tests carried out in order to exclude contraindications. Provide information (if there is any) about important symptoms which may be masked by the medicinal product or if the medicinal product influences laboratory values. If relevant, reference should be made here to possibilities for intolerance to various materials (e.g. disposable plastic syringes), which must be used as part of the medicinal product.]*

- *[Refer to the need for the avoidance of external influences, such as sunlight after the use of phototoxic medicinal products. Other warnings concerning for example other diseases and the influence of the medicinal product on behaviour should be described. Statements should also include for example, reference to discolorations of underwear as a result of changes in the colour of urine and stool.]*

Inference with daily activities

- *[Include whether X may be affected with mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.]*

- *[In the case of anaesthetic medicinal products or medicinal products used for conscious sedation, the above applies for 24 hours. The patient should not make any legal I contractual decisions or drink alcohol for that period of time.]*

Competitive Sport

- *[If relevant, include whether the medicinal product may lead to a positive test for a prohibited substance in competitive sport activities.]*

Children <and adolescents>

- *[When the medicinal product is indicated in children, the special warnings and precautions which are specific to this population (and identified as such in 'Special warnings and precautions for use' of the SmPc) should be included under this sub-heading. Where relevant, parents / caregivers should also be alerted in this section of potential children / teenager specific warnings included under "driving and using machines".]*
- *[If there is no indication in some or all subsets of the paediatric population, information should reflect the paediatric subsection of 'Posology and method of administration' of the SmPC], e.g.* "Do not give X to children between the ages of x and y <years> <months> because <of the risk of […]> <it does not work> <the potential benefits are not greater than the risks>, <it is unlikely to be safe>".

Taking / Giving / Using other medicinal products with X:

- *[The following statement must be included:]*
    - Always tell your healthcare professional if you are taking any other medicinal product. (This includes complementary or traditional medicinal products.)

- *[Describe the effects of other medicinal products on the medicinal product in question and vice versa. Reference should be made to the intensification/weakening and the prolonging/shortening of effects. This information should be in line with the INTERACTIONS as in the SmPC.]*

Taking / Using / Receiving X with food and drink:

- *Interactions not related to medicinal products should be mentioned here. For example, patients should not consume milk in combination with tetracyclines and no alcohol should be consumed during treatment with benzodiazepines and other central nervous system depressants.]*

Pregnancy, Breastfeeding and Fertility:

- *[Include information given in the SmPC, in patient-understandable language. The following additional statement must be included:]*

- If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking this medicinal product.

Driving and using machines

- *[Include whether the medicinal product may affect mental and / or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and / or sound coordination and vision e.g. driving, riding, flying, sailing, operating machines / equipment.]*
    - It is not always possible to predict to what extent X may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which X affects them.

Important information about some of the ingredients of X:

- *[If appropriate, details of those excipients for which it is important for the safe and effective use of the medicinal product. Information on intolerances to excipients (e.g. lactose monohydrate), including alcohol should be provided. Indicate "sugar free" if applicable.]*

3. HOW TO TAKE / USE X

- Do not share medicinal products prescribed for you with any other person.

- *[The following statements should be included, where applicable:]*
    - Always take X exactly as your doctor has instructed you. You should check with your doctor, pharmacist, nurse or any other healthcare professional if you are unsure.
    - The usual dose is...

- *[For medicinal products available only with a prescription, a statement such as the following should be included:]*
    - Your doctor will tell you how long your treatment with X will last. Do not stop treatment early because … If you have the impression that the effect of X is too strong or too weak, tell your doctor or pharmacist.

- *[For medicinal products available without prescription:]*
    - <Always <take> <use> [PRODUCT NAME] exactly as described in this leaflet or as your <doctor> <,> <or> <pharmacist> <or nurse> <has> <have> told you. Check with your <doctor> <or> <,> <pharmacist> <or nurse> if you are not sure.>

- *[For medicinal products available without prescription:]*
    - *In particular, and if at all possible, for medicinal products available without a prescription, precise statements should be included on the usual duration of the therapy, the maximum duration of the therapy and intervals with no treatment, together with clear guidance on when to consult a doctor.]*

- *[The instructions for proper use and the intended dosage ranges (individual and daily doses separately), as well as the maximum daily dose, the frequency, method, route of administration and the duration of treatment, should be stated if relevant. In addition, it may be necessary to explain the route of administration in consumer-intelligible language.]*

- *[Instructions should:*
  - *be used to tell patients what to do. They should not be used to justify or explain an action.*
  - *be described in a practical manner.*
  - *tell patients how to use the medicinal product properly.*
  - *be positive rather than negative, whenever possible. Negative instructions should only be used when the consumer should avoid specific actions.*
  - *be given as separate instructions when the consumer is to carry out two separate actions. Separate actions should not be compressed into a single sentence.*
  - *be numbered and put into the exact order that the consumer should follow.*
  - *usually be intelligible without explanations, so as not to overburden patients with information.] [Explanations should be used to expand on the reasons for instructions and not to give further information. Instructions may be presented in italics or other type with explanations in plain type, so as to give patients a guide as to the significance of the information.]*

- *[When applicable, there should be descriptions (if useful with illustrations) of opening techniques for child-resistant containers and other containers to be opened in an unusual manner.]*
- *[Some examples of statements that may be included here:]*
  - Take the tablets with a sufficient quantity of liquid (e.g. one glass of water)
  - …one or two tablets (500 to 1 000 mg of paracetamol) three times a day, this means a daily maximum of six tablets (3 000 mg of paracetamol)'
  - …in the morning, at lunchtime, immediately before meals, with food, after food'
  - Do not swallow
  - Do not chew
  - Shake well before use
  - Dissolve the effervescent tablet in one glass of water. Then drink the contents of the whole glass'
  - Take X once a day, every day, at about the same time each day
  - Taking your tablets at the same time each day will have the best effect on your blood pressure. It will also help you remember when to take the tablets
  - Allow to reach room temperature before using (e.g. insulins)

- *[For medicinal products not self-administered] The route of administration should be included; Include*
  - You will not be expected to give yourself X. It will be given to you by a person who is qualified to do so.

If you take / use / more X than you should:

- *[Description of signs and symptoms of over dosage that the patient is able to recognize and actions to be taken]; The following statement must be included:*
  - In the event of over dosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control center.
- *[For medicinal products not self-administered]; The following may be acceptable:*
  - Since a healthcare professional will administer X, he/she will control the dosage. However, in the event of over dosage your doctor will manage the over dosage.

If you forget to take / missed a dose of X:

- *[Provide clear explanations of what should be done following irregular use of the medicinal product, e.g. Do not take / receive a double dose to make up for forgotten individual doses.*
- *[For medicinal products not self-administered]; The following may be acceptable:*
  - Since a healthcare professional will administer X, it is unlikely that the dose will be missed.

If you stop taking/using X:

- *[Indicate any effects of interruption or ending treatment early, if applicable. Indicate withdrawal effects when the treatment ends, if applicable]*
  - If you have any further question on the use of X ask your doctor, pharmacist, nurse and healthcare professional

4. POSSIBLE SIDE EFFECTS

- *[A description of the side effects should be provided. Begin this section with:]*
  - X can have side effects.

- *[The following statement must be included:]*
  - Not all side effects reported for X are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking X, please consult your doctor, pharmacist or other healthcare professional for advice.

- *[Describe, if necessary, the actions to be taken. If the patient needs to seek help urgently use the term 'immediately'; for less urgent conditions use the phrase 'as soon as possible'.]*

- *[The information given on side effects should be in accordance with the SmPC. Side effects should be subdivided according to seriousness and frequency, or according to symptom type. Wherever possible, for all side effects the frequency with which they occur must be mentioned to allow patients to know the risk. Irrespective of their frequency, very serious, side effects of the medicinal product should be mentioned first or specially emphasized. This applies in particular to side effects where there is an urgent need to take action.]*

- *[The risk (frequency) of side effects may be presented using the terms "frequent" or "less frequent" if the information is available in the corresponding SmPC. Descriptors such as "common", "rare", etc. should not be used.]*

- *The following is an example of side effects grouped according to seriousness:]*

- If any of the following happens, stop taking X and tell your doctor immediately or go to the casualty department at your nearest hospital:
  - 'swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing',
  - 'rash or itching',
  - 'fainting'

- These are all very serious side effects. If you have them, you may have had a serious reaction to X. You may need urgent medical attention or hospitalization. Tell your doctor, pharmacist, nurse or healthcare professional immediately or go to the casualty department at your nearest hospital if you notice any of the following:
  - chest pain,
  - angina,
  - changes in the way your heart beats, for example, if you notice it beating faster,
  - difficulty breathing,
  - signs of recurrent infections such as fever or sore throat,
  - less urine than is normal for you,
  - yellowing of the skin and eyes, also called jaundice.

- These are all very serious side effects. You may need urgent medical attention. Tell your doctor if you notice any of the following:

  <u>Frequent side effects:</u>

  - nausea (feeling sick),
  - abdominal cramps or stomach pains,
  - headache,
  - dizziness,
  - tiredness,
  - light-headedness,

  <u>Less frequent side effects:</u>

  - dry cough,
  - muscle cramps,
  - flatulence or wind,
  - diarrhoea,
  - loss of appetite.

- Should there be side effects that occur at the beginning of the treatment and then subside or that only occur after prolonged treatment, these are to be mentioned here.

- *[Close this section with:]* If you notice any side effects not mentioned in this leaflet, please inform your doctor, pharmacist, nurse or healthcare professional.

- **Reporting of side effects**
  If you get side effects, talk to your <doctor><or><,><pharmacist><or nurse>. <u>This includes any possible side effect not listed in this leaflet</u>. By reporting side effects, you can help provide more information on the safety of [PRODUCT NAME].
  -

5. HOW TO STORE X

- *[The following statement must be included in this section:]*
  - Store all medicinal products out of sight and reach of children.

- *[Where applicable, the following statements may be included:] [Storage conditions have to concur with that approved in the SmPC*
  - Store at or below X 0C [Explain ideal storage environment]
  - Store at 2ºC – 8ºC (in a refrigerator)
  - Store in a freezer
  - Do not refrigerate / freeze [as appropriate]
  - Store in the original package / container
  - Keep the container in the outer carton
  - Keep the container tightly closed

- *[An additional short explanation of the storage conditions, in patient-friendly terms, should be included when appropriate, e.g.:]*
  - Protect from light / moisture
  - Do not store in a bathroom
  - Do not use after the expiry date stated on the label / carton / bottle

- *[Where applicable, shelf life after reconstitution, dilution or after first opening the container should be indicated]*
- *[Where appropriate, include a warning against any visible signs of deterioration]*
  - Do not use X if you notice (description of the visible signs of deterioration*)*
- *[Information on how to dispose of unused medicinal product, e.g.:]*
  - Return all unused medicinal product to your pharmacist.
  - Do not dispose of unused medicinal product in drains or sewerage systems (e.g. toilets).

6. CONTENTS OF THE PACK AND OTHER INFORMATION
What X contains:

- The active pharmaceutical ingredient(s) is (are)… - The other ingredient(s) is (are)... **What X looks like and contents of the pack:** • *[A physical description, e.g., shape, colour, texture, imprint, etc., of the dosage form should be included here in accordance with the SmPC Information.]* • *[In accordance with information provided in the SmPC, include the pharmaceutical form, the number, volume or mass per package unit, pack size and a description of the packaging material, e.g., bottle, blister pack, etc.]* **Marketing Authorisation Holder and Manufacturer** • *[As in the SmPc]*
7. REGISTRATION NUMBER/MARKET AUTHORISATION NUMBER • *[As in the SmPC]*
8. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION • *[As in the SmPc]*
9. DATE OF REVISION OF THE TEXT • *[As in the SmPc]*

9 PRODUCT LABELLING

9.1 Minimum Information for Medicinal Product Label

- Minimum information required on the outer packing (or secondary packaging) and the immediate packaging (primary packaging) includes:
- the (brand) name of the medicinal product;
- the name(s) (generic name) of all active ingredients in the medicinal product;
- the quantity or proportion of all active ingredient(s) in the medicinal product per dosage unit;
- the name of the dosage form;
- the content of the medicinal product package expressed in the appropriate unit or volume of the medicinal product;
- the batch number of the medicinal product;
- The date of manufacture and the expiry date of the medicinal product;
- the requirements regarding the manner in which the medicinal product shall be stored with specific reference to the applicable storage temperature and other precautions required for the preservation of the medicinal product;

- The name and address of the manufacturer. If your medicinal product has more than one approved site(s) of manufacturer only the site from which the medicinal product was manufactured should be included;
- the name of the holder of certificate of registration of the said medicinal product;
- where applicable, the instruction 'Shake the bottle before use';
- where applicable, the statement: 'For external use only';
- in the case of eye drops or artificial tear solutions in respect of which evidence concerning the self-sterilising ability of the medicinal product has not been approved by the authority the warning 'Do not use more than 30 days after opening';
- the warning: 'Keep out of sight and reach of children';
- the name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicinal product as a preservative;
- the approved name of any anti-oxidant contained in the medicinal product;
- in the case of a medicinal product intended for injection by a particular route of administration only, that route of administration by means of suitable words or abbreviations;
- if the medicinal product requires some preparation, such as dissolving, suspending, diluting or reconstituting before use - instructions for its preparation and, where relevant, a statement of the conditions of storage and the maximum period of storage between preparation and use;
- relevant warning statements, where these are required in relation to a particular medicinal product e.g. list of excipients known to be a safety concern for some patients i.e. contains tartrazine, alcohol, sugar etc. any warning should be in a different colour to the colour used for the rest of the text;
- Approved indications where practical, for use of the medicinal product;
- The recommended dosage of the medicinal product, where practical;
- The name and percentage of preservative contained in the cream, ointment, gel or power should be specified on the immediate container/inner label;
- For active ingredients that are present as salts, hydrates or solvates, it is recommended that the applicant/market authorisation holder includes the name of the salt, hydrate or solvate form on the secondary packaging label;
- The matrix barcode may be included if online access is one of the methods of product information dissemination selected.

Example	Recommendation

The active ingredient is present as the salt of a base or acid and it is established that the strength is labelled in terms of the formulated amount of that salt.	Use the name of the salt on all labels (e.g. metformin hydrochloride 500 mg and raloxifene hydrochloride 60 mg).
The active ingredients are present as a hydrate or solvate (such as dapagliflozin propanediol monohydrate), where the strength of the medicinal product is expressed on the solvent-free basis.	Include the hydrate or solvate in brackets, as in the case for a salt, e.g. dapagliflozin 10 mg (as propanediol monohydrate). If the available label space precludes this on the primary packaging label, you may omit the name of the solvate (e.g. dapagliflozin 10mg) and include it on the secondary packaging label

- The registration number of the medicinal product and general classification for supply i.e. category for distribution/scheduling status.

NOTE: For medicinal products that differ in strength, but otherwise have the same name, colour may be used to emphasise the strength, so as to differentiate between different labels. When the innovator medicinal product uses colour differentiation, it is recommended to sponsors of generic medicinal products to use the same colour scheme as the innovator to differentiate the strengths of their products.

9.2 Medicinal Product Label for Containers Less or Equal to 10ml Capacity

- For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain
- the (brand) name of the medicinal product;
- the name(s) (generic name) of all active ingredient(s) in the medicinal product per dosage unit;
- the quantity or proportion of all active ingredients in the medicinal product;
- the name of the dosage form;
- the content of the medicinal product package expressed in the appropriate unit or volume of the medicinal product;
- the batch number of the medicinal product;
- the expiry date of the medicinal product;
- The name and address of the manufacturer, company or person responsible for placing the product on the market, or a logo that unambiguously identifies the company. If your product has more than one approved site(s) of manufacturer only the site from which the product was manufactured should be included;
- Directions for use, and any warnings or precautions if necessary;

- Route of Administration should be included on the immediate container/inner label of an injectable irrespective of what is included on the outer carton
- For active ingredients that are present as salts, hydrates or solvates, we recommend that you include the name of the salt, hydrate or solvate form on the secondary packaging label;
- The matrix barcode may be included if online access is one of the methods of product information dissemination selected;

Example	Recommendation
The active ingredient is present as the salt of a base or acid and it is established that the strength is labelled in terms of the formulated amount of that salt.	Use the name of the salt on all labels (e.g. metformin hydrochloride 500 mg and raloxifene hydrochloride 60 mg).
The active ingredients are present as a hydrate or solvate (such as dapagliflozin propanediol monohydrate), where the strength of the medicinal product is expressed on the solvent-free basis.	Include the hydrate or solvate in brackets, as in the case for a salt, e.g. dapagliflozin 10 mg (as propanediol monohydrate). If the available label space precludes this on the primary packaging label, you may omit the name of the solvate (e.g. dapagliflozin 10mg) and include it on the secondary packaging label.

- The registration number of the medicinal product and general classification for supply i.e. category for distribution/scheduling status. For products in containers of less than or equal to 10 ml, this information may be included on the matrix barcode.

9.3 Product Label for Blisters, Strips, 1ml or 2ml vials/ampoules and Other Small Containers

- For blisters, strips, 1ml or 2ml vials/ampoules and other similar small containers that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain:
- the (brand) name of the medicinal product
- the name(s) (generic name) of all active ingredients in the medicinal product
- the quantity or proportion of all active ingredient(s) in the medicinal product per dosage unit
- the name of the dosage form
- the batch number of the medicinal product
- the expiry date of the medicinal product
- For active ingredients that are present as salts, hydrates or solvates, we recommend that you include the name of the salt, hydrate or solvate form on the secondary packaging label

Example	Recommendation
The active ingredient is present as the salt of a base or acid and it is established that the strength is labelled in terms of the formulated amount of that salt.	Use the name of the salt on all labels (e.g. metformin hydrochloride 500 mg and raloxifene hydrochloride 60 mg).
The active ingredients are present as a hydrate or solvate (such as dapagliflozin propanediol monohydrate), where the strength of the medicinal product is expressed on the solvent-free basis.	Include the hydrate or solvate in brackets, as in the case for a salt, e.g. dapagliflozin 10 mg (as propanediol monohydrate). If the available label space precludes this on the primary packaging label, you may omit the name of the solvate (e.g. dapagliflozin 10mg) and include it on the secondary packaging label

- The registration number of the medicinal product and general classification for supply i.e. category for distribution/scheduling. For medicinal products in containers blisters, strips, 1ml or 2ml and other small containers, this information may be included on the matrix barcode.

It is recognised that blister strips are often cut up, even if there is no intention for individual dosage units to be supplied in this way. To help ensure the quality and safe use of these medicinal products, repeating the required information at least once every two dosage units whenever possible is recommended.

It is also recommended that the particulars on the label remain visible until the last dose is removed. This may best be achieved using a random display where the information appears frequently across the blister strip.

10 LANGUAGES

The working languages of SADC are English, French, Portuguese and Swahili and such other languages as the SADC Council may determine. The product information must be in a working language(s) of the member state(s) where the medicinal product is intended to be placed on the market.

11 PRODUCT SAMPLES

- Presentation of medicinal product samples at the time of application for market authorisation is required;
- At the time of application of market authorisation, a sample of the medicinal product in the intended final container should be provided and not necessarily with the proposed label.

- Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalised. Colour copies of the actual proposed labels should be submitted;
- In cases where there is acceptable justification for a waiver e.g.- medicinal products that require special handling, mock-ups of the labels can be provided;
- Erasable or pealable labels are not acceptable. Any information that is required on the label should be accessible without having to peel the label from the container. Only permanent ink should be utilized when printing the product label.

12 LIST OF REFERENCES

European Commission Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use revision 1 12th January 2009 *http://ec.europa.eu/health/files/eudralex/vol2/c/2009_01_12_readability_guideline_final_en.pdf)*

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