SOUTHERN AFRICAN DEVELOPMENT COMMUNITY

GUIDELINE ON PRODUCT INFORMATION AND LABELLING

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Draft for Comments

Please send any comments you may have to the SADC MRH Project Coordinator (sadcproject@mcaz.co.zw) with copies to Mr F. Masekela (fmasekela@mcaz.co.zw) and Mrs E. Sebua (esebua@bomra.co.bw) by **16 August 2019.** Comments should be compiled on the accompanying table-for-comments.

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Introduction

Southern African Development Community (SADC), as a region has harmonized medicines registration guidelines in the common technical document (CTD) format that were approved in January 2015.[1] 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),[2]which supports the pharmaceutical component in the SADC Industrialization Strategy and Roadmap 2015 – 2063.[3] Moreover, this supports the priority areas of creating an enabling regulatory environment and strengthening medicines regulatory capacity in the approved SADC Pharmaceutical Business Plan 2015 – 2019.[4]

Taking into account the need for stakeholder engagement in drafting regulatory guidelines, a workshop with industry and regulators was held 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 marketing authorization holders to ensure that all product information is of high quality when submitted to SADC member states as part of applications for new marketing authorizations or updates to existing marketing authorization;

(iii) Enable marketing authorization holders to ensure that the critical product information necessary for the safe use of the medicine is included;

[1]SADC, Records of the meeting of the SADC Ministers of Health & Ministers Responsible for HIV and AIDS, January 2015, Victoria Falls, Zimbabwe

[2]SADC Strategy on Regional Manufacturing of Essential Medicines and Health Commodities (2016-2020) (draft-unpublished)

[3]SADC Industrialization Strategy and Roadmap 2015-2063, April 2015

[4]SADC Pharmaceutical Business Plan 2015 - 2019

(iv) Enable marketing authorization 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.

1. 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 marketing authorization 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 medicines (innovator). They also have equal applicability to medicines that require a prescription and those available over the counter. The guidelines have primarily been developed to apply to medicines for human use; they however may be used for veterinary medicines depending on the country context. It is acknowledged that when used for veterinary medicines certain aspects of the guideline would require reviewing and alignment.

2. Glossary

2.1 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
The person or company that applies for registration, licensing or marketing authorization of a new pharmaceutical product or an update or variation to an existing marketing authorization.

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.

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/Schedule
Listing or placing of medicinal products in different groups in accordance with 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
The non-proprietary name/brand name which is widely and internationally used.

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

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 accurately and convenient delivery of 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
Any medicine whose use does not need the direction or prescription by a health care provider.

Generic Name
International non-proprietary name recommended by the World Health Organization.
Alternatively, you can check one of these definitions:

• The chemical name of medicine,
• A term referring to the chemical makeup of a drug rather than to the advertised brand name under which the medicine is sold,
• A term referring to any medicine marketed under its chemical name without advertising,
• The name of the active ingredients as distinct.

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

Indications of the Product (synonymous with Therapeutic Indication)
A narrative identification of a well-defined disease state, syndrome or clinical applications of a pharmaceutical product.

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

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

I**nternational Non-proprietary Name**
A generic name, publicly owned internationally, that identifies active ingredient (s)/substance(s) of pharmaceutical product in existence worldwide.

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

Marketing Authorization
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 authorization is based, approved product information` and address and name of the holder of the authorization, and the period of validity of the authorization.

Market Authorization Holder
A person or company in whose name the marketing authorization has been granted.

Medicine

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 medicines affecting each other either pharmacodynamically or pharmacokinetically or both.

Multisource (Generic) Pharmaceutical
Product multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent or bioequivalent.

Package Insert
Package insert means a leaflet containing information for the prescriber, the dispenser and the end user.

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 and veterinary subjects.

Pharmaceutical Product
Any preparation for human or veterinary 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 medicines.

Pharmacy only (Medicines)
An intermediate level of control, medicines that can be bought only from pharmacies and under a pharmacist's supervision.

Precaution(s) for Use
Special care to be exercised by prescriber and patient in the 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 authorization holder. This would include the Summary of product characteristics (SmPC) and Patient information leaflet (PIL).

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.

Registration Number
A number assigned to a medicinal product after being given marketing authorization.

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 that 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 medicine.

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)
The SmPC is a legal document approved as part of the marketing authorization of each medicine. It is the basis of information for healthcare professionals on how to use the medicine.

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).

3. Product information

The product information is important for the safe use of the product by health care professionals as well as the patients or users and 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 marketing authorization 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), which is also commonly referred to as package insert (PI), intended for health care professionals, (ii) patient information leaflet (PIL) intended for the patient or user and (iii) product labelling was adopted.

4. Dissemination and Accessibility of Product Information

In most SADC countries, information for health care professionals is normally referred to as the package insert (PI); this is distributed within the packaging of the product. Essentially the structure of this package insert is similar to what is identified as the SmPC in Europe.
The options for the distribution and subsequent accessibility of product information include:

- With the product
- Online (electronic compendium),
- Mobile application (compendium)
- Compilation /book
- Disseminated separately

These options for the distribution of the product information should be approved by the regulatory authority.

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 authorization holder
- The market authorization holder should ensure that the SmPC of the product is disseminated and therefore accessible to the health care professional in at least three (3) of the five (5) possible mechanisms. This is in order to ensure that all the health care 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 health care professionals in the region i.e. there are those health care 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;
- Reference books/formularies should be made available as part of the regulatory requirements for licensing;
- The SmPC should be included in the package for products to be administered by a health care practitioner e.g. injections;
- A separate SmPC per strength and per pharmaceutical form, containing all pack-sizes related to the strength and pharmaceutical form concerned is required;
- Combined SmPC depend on indications/posology of the product.

2. Accessibility of the PIL:

- The PIL should be included within each package of the product and the same should be available online.
- “In principle“ a separate PIL for each pharmaceutical form and each strength is required.

3. Further Guidance on Product Information Accessibility:
    - Accessibility of the product information is dependent on the type of each product e.g. medicines for hospital use or for administration by health care professional may not need PIL in the pack.
    - "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 access may also be facilitated by QR code on the product label.

5. Summary of Product Characteristic (SmPC)

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

1. Name of the medicinal product:
    - This should be the proprietary name of the product as approved by the licensing 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 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 medicine.
    - 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 (active substances):

- 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 “.
- All excipients should be qualitatively included in this section except excipients as well as acids and bases used for pH adjustment and not present in the final product
- Medicines intended for oral administration should indicate whether or not they contain sugar, e.g. “contains sugar” or” sugar free”, 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 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 section on definitions and examples in Appendix 1 of this guideline

3. Pharmaceutical form:

- Applicants should state pharmaceutical forms in line with guidance contained in the European Directorate for the Quality of Medicines (EDQM) database.
- A visual description of the appearance of the product (e.g. colours, markings) should be provided.
- 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 should not deviate from the innovator’s clinical particulars unless they have included scientific data to support the claim(s). The MAH 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

4.1 Therapeutic indications:

- Applicants should clearly and concisely define the proposed target disease and population for the medicine as applied for, 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 known to be eradicated by the medicine, where this information is available.
- Specify if product is exclusively for paediatric use.

4.2 Posology and method of administration:

- For each route of administration and indication include:
    - Dose and dose interval
    - The intake of the medicine in relation to food intake
    - 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 adjustment for each age category where appropriate
    - Special populations: dosage adjustment with renal insufficiency, liver disease, dialysis, concomitant disease or interactions requiring specific dose adjustments
    - 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 medicine in relation to food intake
    - If necessary, relevant instructions for correct administration/use, including the use of devices
    - Where relevant, instructions on how to reconstitute the medicines
    - For products to be reconstituted, the storage condition and shelf life for reconstituted solutions or suspensions should be stated
    - For parenteral preparations: Include information on compatible and incompatible solutions where this may be necessary for administration purposes
    - For extemporaneous preparation: Detailed instructions for use, e.g. for dispersible or parenteral formulations and instructions for extemporaneous preparation in section 6.6.

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 medicine or class of medicines).
- Where the use of a medicine may be life threatening, cause mortality or serious morbidity.
- Medicines or classes of medicine 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 medicine) for not using the combination. (Cross-reference to INTERACTIONS.)
- 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. (See WARNINGS and Special Precautions).
- 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 WARNINGS AND SPECIAL PRECAUTIONS.)
- For combination products, the contraindications for APIs must be presented for the combination.
- Contraindications to be presented in bullet format where relevant.

4.4 Warnings and special 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 warnings and special precautions.
- Relative contraindications are conditions under which use of the medicine could be acceptable, provided that special conditions for use are fulfilled.
- Special patient groups likely to experience medicine 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 clearance (micromol/L)"

- hepatic impairment (include the degree of impairment).
- 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 medicine, 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. If dose reduction is recommended in such circumstances, this should be included under DOSAGE AND DIRECTIONS FOR USE 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.)
- Patient populations not studied in the clinical trial programme and for which there is no information available, where this is clinically relevant.
- Any adverse reactions referred to in this section or known to result from conditions mentioned in this section must also be included under 'Side Effects'.
- Descriptions of warnings and precautions regarding pregnancy and lactation should be addressed under the heading PREGNANCY AND LACTATION HUMAN REPRODUCTION.
- 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 INTERACTIONS.
- Include adverse reactions which apply to the therapeutic, chemical or pharmacological class, which may not have been observed yet in relation to the medicine, 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 Side 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 medicines or medicines 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.
- Effects of the disease itself on these abilities should not be discussed. For the latter two situations, warnings/special precautions for use should be mentioned. If not shown to be safe only the statement "Safety has not been established" will be allowed.
- For combination products the contraindications for APIs must be presented for the combination.
- Include risk management/minimization measure were relevant.
- If relevant, include whether the medicine may lead to a positive test for a prohibited substance in competitive sport activities.
- Any special precaution necessary relating to excipients.

4.5 Interactions:

- Applicants should include information on potentially clinically relevant interactions based on the pharmacology (pharmacodynamic properties and preferably in vivo pharmacokinetic properties) of the medicine, particularly on interactions which result in a recommendation regarding the use of the medicine.
- 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 medicine, cross- referencing to DOSAGE AND DIRECTIONS FOR USE and/or to WARNINGS AND SPECIAL PRECAUTIONS.
- 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 medicine concerned (in the package insert) should be given first, followed by interactions resulting in clinically relevant changes on the use of other medicines.
- 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 WARNINGS AND SPECIAL PRECAUTIONS)
- Precautions regarding dose adjustment (cross reference to DOSAGE AND DIRECTIONS FOR USE and to WARNINGS AND SPECIAL PRECAUTIONS), stating specific situations where these may be required. For the actual dose recommendation, cross reference [refer] to DOSAGE AND DIRECTIONS FOR USE.
- 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 medicine requires adjustment of the doses of concomitant (interacting) medicines, e.g. if a medicine is an enzyme inhibitor or inducer
- the need for a washout period when using medicines consecutively.

o 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.
o Results demonstrating an absence of interaction should only be mentioned if this is likely to be major clinical interest to the prescriber
o Include interactions with laboratory tests and investigations.
o If no interactions studies have been performed, this should be stated.
o For combination products the interactions for individual active pharmaceutical ingredient must be stated and characterised according to severity.
o Additionally, potential medicine 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.
o Where too numerous, a tabular format may be preferable for ease of reference, e.g. antivirals".

4.6 Fertility, pregnancy and lactation:

o 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 if she and/or her partner are on treatment with medicine{s)
- known to be teratogenic, or cause embryo or foetal harm.

- 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 medicine 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).

- Lactation:
  - 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 medicine while breast-feeding or, alternatively, whether or not mothers taking or using the medicine should breastfeed.

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 medicine 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.
- 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]

interference with daily activities, include, as appropriate, the statement: specify whether the medicine has:

- no or negligible influence
- minor or moderate influence
- major influence on these abilities.

- 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

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 medicine.
- 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 medicines, 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 package inserts 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 package insert 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 medicines, 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 Interactions.]
- [Include adverse reactions which apply to the therapeutic, chemical or pharmacological class, which may not have been observed yet in relation to the medicine, 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.]

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 SIDE EFFECTS).
- Describe recommended management of overdose e.g. [symptomatic] treatment is symptomatic and supportive or in relation to specific agonists/antagonists or methods to increase elimination of the medicine e.g. dialysis (excluding gastric lavage)

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 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.

5.2 Pharmacokinetic properties:

- 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, protein binding, biotransformation, elimination and linearity/non- linearity, as appropriate for the dosage form of the medicine marketed.
- Include information on the intake of the medicine in relation to food intake (i.e. with or without food).
- Include characteristics in specific patient groups with respect to factors such as age, 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.
- Excipients with known effect should have a separate warning, e.g. lactose.

6.2 Incompatibilities:

- Physical/chemical incompatibilities, when likely to be mixed/co-administered.

6.3 Shelf life:

- Clear statement in appropriate unit of time.
- (In-use shelf life: with storage conditions after opening).
- 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.'

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).

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

- only information for health personnel,
- preparation (reconstitution) and special disposal (e.g. cytotoxics).

7. Marketing Authorisation Holder Particulars:

- Different terminology and responsibility in Member States. Agreed to use MAH – i.e. the person/company with legal responsibility to place the product on the market.
- The manufacturer(s) of the product should be listed on the SmPC. This could be an extra heading "Manufacturer(s)" if different from the MAH.All the approved manufacturing site(s) should be listed on the SmPC.

8. Marketing Authorisation (Registration) Number:

- All applicable registration numbers should be listed.

9. Date of first authorisation /renewal of the authorisation:

- This may be the date of first authorisations in the SADC region i.e. first marketing authorisation within the SADC Member States??

10. Date of revision of the text:

6. Patient Information Leaflet (PIL)

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 medicine would require that the latest approved SmPC also be submitted.
- For new medicine 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.
- An electronic copy (MSWord document) of the SmPC and the PIL should be included on an appropriate electronic storage device.

2. Legibility of the PIL:

2.1 Print size and type:

- The information appearing in the PIL to be provided to the patient should be printed in a type having a minimum legibility (e.g. Helvetica 10).

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 medicine.

  For example:

  Tell your doctor or pharmacist 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.
- 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 medicine, provided the context clarifies what the pronoun refers to.

3. Format of the PIL

3.1 Headings

- Headings and sub-headings in the PIL and the order of the headings should be in line with the model template (see Section 7 under PIL of this document).
- Headings and sub-headings should be made conspicuous.
- More than two levels of headings may impair legibility.

3.2 Content

- The information contained in the PIL must be in accordance with the SmPC for the medicine
- 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.

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) medicine measureful...*' where a medicine 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 medicines (e.g. those which 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.

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 medicine falling in two different categories of distribution/schedules, a separate package insert should be submitted for each category of distribution/schedule.

4. MODEL PIL

This section contains a model template for developing a Patient Information Leaflet. Applicants 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 should adapt e.g. for the relevant pharmaceutical dosage form, route of administration or population for which the medicine 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 medicines, 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 [] medicine.*
- *In the case of a complementary medicine the following shall be included*:

- *a statement identifying the discipline of the medicine; and*
- *if the medicine has not received registration with any regulatory authority the disclaimer "This medicine has not been evaluated for safety and efficacy by a regulatory authority. This medicine is not intended to diagnose, treat, cure or prevent any disease."*

CATEGORY OF DISTRIBUTION/SCHEDULING STATUS

- *[The category of distribution/scheduling status of the medicine as it appears in the SmPC]*

PROPRIETARY NAME AND DOSAGE FORM

- *[The proprietary name of the medicine (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 Package Insert).*
- *[For medicines 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 medicine with other people. It may harm them, even if their symptoms are the same as yours. (May be omitted if the medicine is not self-administered*).*
- *[For medicines 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 CONTAINS

- *[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].

2. WHAT X IS USED FOR

- *[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 medicine].*

3. BEFORE YOU TAKE / USE / ARE GIVEN / ADMINISTERED X

3.1 Do not take / give / use / 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 Package Insert, 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 medicines, 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.

3.2 Take special care / Special care should be taken with X:

- **<u>Tell your doctor or healthcare professional before being given the injection if:</u>**
  - 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 medicine 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 medicine or if the medicine 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 medicine.]*

- *[Refer to the need for the avoidance of external influences, such as sunlight after the use of phototoxic medicines. Other warnings concerning for example other diseases and the influence of the medicine 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 medicines or medicines 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 medicine may lead to a positive test for a prohibited substance in competitive sport activities.*

3.3 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 medicine. Information on intolerances to excipients (e.g. lactose monohydrate),*

including alcohol should be provided. Indicate "sugar free" if applicable.]

3.4 Taking / Giving / Using other medicines with X:

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

  - *[Describe the effects of other medicines on the medicine 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 Package Insert.]*

3.5 Pregnancy and Breastfeeding:

- *[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 medicine.

4. HOW TO TAKE / USE / RECEIVE X

Taking / Using / Receiving X with food and drink:

- *Interactions not related to medicines 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.]*

- Do not share medicines 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 or pharmacist if you are unsure.
  - The usual dose is...

- *[For medicines 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 medicines available without prescription:*

  - *In particular, and if at all possible, for medicines 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 medicine 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 medicines 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 overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.
- *[For medicines 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 overdosage your doctor will manage the overdosage.

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

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

Effects when treatment with X is stopped:

[Indicate any effects of interruption or ending treatment early, if applicable. Indicate withdrawal effects when the treatment ends, if applicable]

5. POSSIBLE SIDE EFFECTS

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

2. X can have side effects.
    - *[The following statement must be included:]*
3. 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 medicine 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 package insert. 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 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 or pharmacist.

6. STORING AND DISPOSING OF X

- *[The following statement must be included in this section:]*
  - Store all medicines out of 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 2°C – 8°C (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 medicine,e.g.:]*
  - Return all unused medicine to your pharmacist.
  - Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF X

- *[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.]*

8. IDENTIFICATION OF X • *[A physical description, e.g. shape, colour, texture, imprint, etc., of the dosage form should be included here in accordance with the Package Insert Information.]*
9. REGISTRATION NUMBER/REFERENCE NUMBER • *[As in the SmPC]*
10. NAME AND ADDRESS OF REGISTRATION HOLDER • *[As in the SmPc]*
11. DATE OF PUBLICATION • *[As in the SmPc]*

7. Product labeling

- Minimum information on the outer packing (or secondary packaging) and the immediate packaging (primary packaging)
  - the (brand) name of the medicine;
  - the name(s) (generic name) of all active ingredients in the medicine;
  - the quantity or proportion of all active ingredient(s) in the medicine per dosage unit;
  - the name of the dosage form;
  - the content of the medicine package expressed in the appropriate unit or volume of the medicine;
  - the batch number of the medicine;
  - the expiry date of the medicine;
  - the requirements regarding the manner in which the medicine shall be stored with specific reference to the applicable storage temperature and other precautions required for the preservation of the medicine;
  - The name and address of the manufacturer;
  - the name of the holder of certificate of registration of the said medicine;
  - 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 medicine has not been approved by the authority the warning 'Do not use more than 30 days after opening';
  - the warning: 'Keep out of reach of children';
  - the name and percentage of any bacteriostatic or bactericidal agent which has been added to the medicine as a preservative;
  - the approved name of any anti-oxidant contained in the medicine;

- in the case of a medicine intended for injection by a particular route of administration only, that route of administration by means of suitable words or abbreviations;
- if the medicine 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 medicine 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 medicine;
- The recommended dosage of the medicine, where practical;
- The QR code (Quick Response Code);
- For active ingredients that are present as salts, hydrates or solvates, it is recommended that the applicant includes the name of the salt, hydrate or solvate form on the main 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 medicine 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, you may omit the name of the solvate (e.g. dapagliflozin 10mg) on labels other than the main label.

- the registration number of the medicine;
- general classification for supply i.e. category for distribution/scheduling status.

NOTE: For medicines 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 medicine uses colour differentiation, it is recommended to sponsors of generic medicines to use the same colour scheme as the innovator to differentiate the strengths of their products.

- **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 medicine;
    - the name(s) (generic name) of all active ingredient(s) in the medicine per dosage unit;
    - the quantity or proportion of all active ingredients in the medicine;
    - the name of the dosage form;
    - the content of the medicine package expressed in the appropriate unit or volume of the medicine;
    - the batch number of the medicine;
    - the expiry date of the medicine;
    - 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;
    - Directions for use, and any warnings or precautions if necessary;
    - the QR-code;
    - 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 main 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 medicine 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, you may omit the name of the solvate (e.g. dapagliflozin 10mg) on labels other than the main label.

    - general classification for supply i.e. category of distribution/scheduling status or category of distribution.

- **For blisters, strips, 1ml or 2ml and other similar small containers as a minimum:**

    - the (brand) name of the medicine
    - the name(s) (generic name) of all active ingredients in the medicine
    - the quantity or proportion of all active ingredient(s) in the medicine per dosage unit
    - the name of the dosage form
    - the batch number of the medicine
    - the expiry date of the medicine
    - 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 main 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 medicine 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, you may omit the name of the solvate (e.g. dapagliflozin 10mg) on labels other than the main label.

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 medicines, ~~it is recommended~~ 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.

8. Languages

Article 37 of Chapter 15 of the SADC Treaty as amended in 2001 stipulates that “The working languages of SADC shall be English, French and Portuguese and such other languages as the Council may determine”. This indicates that for any product that is intended for the SADC

market, the manufacturer should ensure that all three languages are available for the SmPC, PIL and label if the product is to be marketed in all the countries within SADC. Exception can be made for products intended for specific markets in the region, in this case the specific language(s) for that/those market/s may be used.

9. Product samples

- Presentation of product information at the time of application for market authorization is required
- Colour copies of the proposed labels should be submitted
- A sample of the product in the intended final container should be provided. In cases where there is acceptable justification for a waiver e.g., products that require special handling, mock-ups of the samples can be provided.
- Erasable or pealable labels are not acceptable

Appendix 1: Excipients and Information for the Package Leaflet[5]

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Aprotinin		Topical	Zero	May cause hypersensitivity or severe allergic reactions.	The topical route in this case refers to sites that may have access to the circulation (e.g. wounds, body cavities etc.).
Arachis oil (peanut oil)		All	Zero	<Medicinal Product> contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	. Purified arachis oil may contain peanut protein. The PhEur monograph does not contain a test for residual protein. SmPC: contraindication.
Aspartame (E 951)	09/10/2017	Oral	Zero	This medicine contains x mg aspartame in each <dosage unit><unit volume><which is equivalent to x mg/<weight><volume>. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.	Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Information to consider for the SmPC: Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age

[5] *Adopted from Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668*

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Azo colouring agents e.g.: Tartrazine (E 102) Sunset yellow FCF (E 110) Azorubine, carmoisine (E 122) Amaranth (E 123) Ponceau 4R, cochineal Red A (E 124) Brilliant black BN, black PN (E 151)		Oral	Zero	May cause allergic reactions.	
Balsam of Peru		Topical	Zero	May cause skin reactions.	
Benzalkonium chloride	09/10/2017	All	Zero	This medicine contains x mg benzalkonium chloride in each <dosage unit><unit volume><which is equivalent to x mg/<weight><volume>.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	09/10/2017	Ocular	Zero	Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.	From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.
Benzalkonium chloride	09/10/2017	Nasal	Zero	Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.	Long-term use may cause oedema of the nasal mucosa.
Benzalkonium chloride	09/10/2017	Inhalation	Zero	Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzalkonium chloride	09/10/2017	Cutaneous	Zero	Benzalkonium chloride may irritate the skin. You should not apply this medicine to the breasts if you are breast-feeding because the baby may take it in with your milk.	Use during pregnancy and lactation is not expected to be associated with harmful effects to the mother as cutaneous absorption of benzalkonium chloride is minimal. Not for application to mucosa.
Benzalkonium chloride	09/10/2017	Oromucosal, rectal and vaginal	Zero	Benzalkonium chloride may cause local irritation.	
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	All	Zero	This medicine contains x mg benzoic acid/benzoate salt> in each <dosage unit><unit volume> which is equivalent to x mg/<weight><volume>.	
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	Oral, parenteral	Zero	<Benzoic acid/Benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	Topical	Zero	<Benzoic acid/Benzoate salt> may cause local irritation	May cause non-immunologic immediate contact reactions by a possible cholinergic mechanism.
Benzoic acid (E 210) and benzoates e.g.: Sodium benzoate (E 211) Potassium benzoate (E 212)	09/10/2017	Topical	Zero	<Benzoic acid/Benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Absorption through the immature skin of neonates is significant.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzyl alcohol	09/10/2017	All	Zero	This medicine contains x mg benzyl alcohol in each <dosage unit><unit volume> which is equivalent to x mg/<weight><volume>. Benzyl alcohol may cause allergic reactions	
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.	Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Warning in the SmPC should be given if used in neonates.
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.	Increased risk due to accumulation in young children.
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
				“metabolic acidosis”).	
Benzyl alcohol	09/10/2017	Oral, parenteral	Zero	Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).	High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
Benzyl alcohol	09/10/2017	Topical	Zero	Benzyl alcohol may cause mild local irritation.	
Bergamot oil (containing bergapten)		Topical	Zero	May increase sensitivity to UV light (natural and artificial sunlight).	Does not apply when bergapten is shown to be absent from the oil.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Boric acid (and borates)	09/10/2017	All	1 mg B/day*	Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future.	* 1 mg B (Boron) = 5.7 mg boric acid. See Q&A document (EMA/CHMP/619104/2013) for further calculations. Amount of boron per age group which may impair fertility if exceeded: Age — Safety limit < 2 years — 1 mg B/day < 12 years — 3 mg B/day < 18 years** — 7 mg B/day ≥ 18 years** — 10 mg B/day ** This amount may also cause harm to the unborn child.
Bronopol		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Butylated hydroxyanisole (E 320)		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.	
Cetostearyl alcohol including Cetyl alcohol		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Chlorocresol		Topical, parenteral	Zero	May cause allergic reactions.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-βcyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated βcyclodextrin (RM-β-CD)	09/10/2017	All	20 mg/kg/day	This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>. Do not use in children less than 2 years old unless recommended by your doctor.	Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC. There is insufficient information on the effects of CDs in children < 2 years old. Therefore, a case by case judgement should be made regarding the risk/benefit for the patient. Based on animal studies and human experience, harmful effects of CDs are not to be expected at doses below 20 mg/kg/day.
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-βcyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated	09/10/2017	Oral	200 mg/kg/day	Cyclodextrins may cause digestive problems such as diarrhoea.	At high doses cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
βcyclodextrin (RM-β-CD)					
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-βcyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated βcyclodextrin (RM-β-CD)	09/10/2017	Parrenteral	200 mg/kg/day and use > 2 weeks	If you have a kidney disease, talk to your doctor before you receive this medicine.	In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins. In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.
Dimethyl sulphoxide		Topical	Zero	May be irritant to the skin.	
Ethanol		Oral, parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per <dose>	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
Ethanol		Oral, parenteral	100 mg per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per <dose>, equivalent to ... ml beer, ... ml wine per <dose>. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5% vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol		Oral, parenteral	3g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per <dose>, equivalent to ... ml beer, ... ml wine per <dose>. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease, or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	
Formaldehyde		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Formaldehyde		Topical	Zero	May cause stomach upset and diarrhea.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Fragrances containing allergens* (See appendix)	09/10/2017	Topical	Zero	This medicine contains fragrance with <allergen(s)>*. <Allergen(s)> * may cause allergic reactions.	*< >: fragrance allergens listed in appendix. In addition to allergic reactions in sensitised patients, non-sensitised patients may become sensitised. Benzyl alcohol is listed as one of the 26 fragrance allergens but can also be used as an excipient. When benzyl alcohol is used as an excipient (in addition to a fragrance or not), the label of this excipient applies.
Fructose	09/10/2017	Oral, parenteral	Zero	This medicine contains x mg fructose in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>.	The additive effect of concomitantly administered products containing fructose (or sorbitol) and dietary intake of fructose (or sorbitol) should be taken into account.
Fructose	09/10/2017	Oral	Zero	*[If the medicine is in contact with teeth (e.g. oral liquids, lozenges or chewable tablets) and is intended for long term use:] Fructose may damage teeth.*	Oral products used frequently or over a long period of time, e.g. for two weeks or longer.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Fructose	09/10/2017	Intravenous (IV)	Zero	If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose in this medicine, which may cause serious side effects. You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.	Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary. Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing fructose) given intravenously may be life threatening and must be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.
Fructose	09/10/2017	Oral, parenteral (either than IV)	5 mg/kg/day	If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.	Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Galactose		Oral, parenteral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicine
Galactose		Oral, parenteral	5g	Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus.	
Glucose		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare glucose-galactose malabsorption should not take this medicine.
Glucose		Oral, parenteral	Zero	Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus.	
Glucose		Oral liquids, lozenges and chewable tablets	5g	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
Glycerol (E 422)		Oral	10 g per dose	May cause headache, stomach upset and diarrhea.	
Glycerol (E 422)		Rectal	1 g	May have a mild laxative effect.	.
Heparin (as an excipient)		Parenteral	Zero	May cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin containing medicines.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Invert sugar		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance or glucose-galactose malabsorption should not take this medicine
Invert sugar		Oral	5g	Contains x g of a mixture of fructose and glucose per dose. This should be taken into account in patients with diabetes mellitus.	
Invert sugar		Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
Lactitol (E 966)		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not take this medicine.
Lactitol (E 966)		Oral	10g	May have a mild laxative effect. Calorific value 2.1 kcal/g lactitol.	
Lactose		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Lactose		Oral	5g	Contains x g lactose (x/2 g glucose and x/2 g galactose) per dose. This should be taken into account in patients with diabetes mellitus.	
Latex Natural Rubber (latex)		All	Zero	The container of this medicinal product contains latex rubber. May cause severe allergic reactions.	Not a typical excipient, but a warning is considered necessary.
Macrogolglycerol ricinoleate (castor oil polyoxyl) Macrogolglycerol hydroxystearate (castor oil polyoxyl hydrogenated)		Parenteral	Zero	May cause severe allergic reactions	
Macrogolglycerol ricinoleate (castor oil polyoxyl) Macrogolglycerol hydroxystearate (castor oil polyoxyl hydrogenated)		Oral	Zero	May cause stomach upset and diarrhea.	
Macrogolglycerol ricinoleate (castor oil polyoxyl) Macrogolglycerol hydroxystearate (castor oil polyoxyl hydrogenated)		Topical	Zero	May cause skin reactions.	
Maltitol (E 965) Isomalt (E 953) (isomaltitol) Maltitol liquid (hydrogenated glucose syrup)		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Maltitol (E 965) Isomalt (E 953) (isomaltitol) Maltitol liquid (hydrogenated glucose syrup)		Oral	10g	May have a mild laxative effect. Calorific value 2.3 kcal/g	
Mannitol (E 421)		Oral	10 g	May have a mild laxative effect.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Ocular	Zero	May cause allergic reactions	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis) and discolouration.	
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Parenteral	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that <you/your child> may experience an allergic reaction. Tell your doctor if <you/your child> have/has any known allergies.	
Organic mercury compounds e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate		Parenteral	Zero	Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.	Additional statement to be mentioned for vaccines
Parahydroxybenzoates and their esters e.g.: Ethyl p-hydroxybenzoate (E 214) Sodium ethyl phydroxybenzoate (E 215) Propyl p-hydroxybenzoate Sodium propyl phydroxybenzoate Methyl p-hydroxybenzoate (E 218) Sodium methyl phydroxybenzoate (E 219)		Oral Ocular Topical	Zero	May cause allergic reactions (possibly delayed).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Parahydroxybenzoates and their esters e.g.: Ethyl p-hydroxybenzoate (E 214) Sodium ethyl phydroxybenzoate (E 215) Propyl p-hydroxybenzoate Sodium propyl phydroxybenzoate Methyl p-hydroxybenzoate (E 218) Sodium methyl phydroxybenzoate (E 219)		Parenteral Inhalation	Zero	May cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.	
Phenylalanine	09/10/2017 *Corrigendum 19/11/2018*	All	Zero	This medicine contains x mg phenylalanine in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>. Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Phosphate buffers	09/10/2017	Ocular	Zero	This medicine contains x mg phosphates in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>. If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.	Corresponding SmPC statement under Undesirable effects: "Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas."
Potassium		Parenteral	Less than 1 mmol per dose	This medicine contains potassium, less than 1 mmol (39 mg) per <dose>, i.e. essentially 'potassium free'.	Information relates to a threshold based on the total amount of K+ in the medicinal product. It is especially relevant to products used in paediatric doses, to provide information to prescribers and reassurance to parents concerning the low level of K+ in the product.
Potassium		Oral, parenteral	1 mmol per dose	This medicine contains x mmol (or y mg) potassium, per <dose>. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.	
Potassium		Intravenous (IV)	30 mmol/l	May cause pain at the site of injection.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	All	1 mg/kg/day	This medicine contains x mg propylene glycol in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>.	
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Oral, parenteral	1 mg/kg/day	If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol	Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Oral, parenteral	50 mg/kg/day	y If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.	Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Oral, parenteral	50 mg/kg/day	If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.	While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Oral, parenteral	50 mg/kg/day	If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine	Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Oral, parenteral	500 mg/kg/day	Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects. Do not use this medicine in children less than 5 years old. Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are taking this medicine.	Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol. Therefore, doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis. Medical monitoring is required.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Cutaneous	50 mg/kg/day	Propylene glycol may cause skin irritation. Do not use this medicine in babies less than 4 weeks old with open wounds or large areas of broken or damaged skin (such as burns) without talking to your doctor or pharmacist	
Propylene glycol (E 1520) and esters of propylene glycol	09/10/2017	Cutaneous	500 mg/kg/day	Propylene glycol may cause skin irritation. Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns) without checking with your doctor or pharmacist.	
Sesame oil		All	Zero	May rarely cause severe allergic reactions.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium	09/10/2017	Oral, parenteral	Less than 1 mmol (23 mg) per dose	This medicine contains less than 1 mmol sodium (23 mg) per <dosage unit><unit volume>, that is to say essentially 'sodium-free'.	1 mmol of sodium (Na) = 23 mg Na = 58.4 mg salt (NaCl). Information relates to a threshold based on the total amount of sodium in the medicinal product. It is especially relevant to products used in children or in patients on a low sodium diet, to provide information to prescribers and reassurance to parents or patients concerning the low level of sodium in the product.
Sodium	09/10/2017	Oral, parenteral	1 mmol (23 mg) per dose	This medicine contains x mg sodium (main component of cooking/table salt) in each <dosage unit><unit volume>. This is equivalent to y% of the recommended maximum daily dietary intake of sodium for an adult.	For parenterals with variable (e.g. weight-based) dosing sodium content may be expressed in mg per vial. Proposed wording for SmPC: "This medicinal product contains x mg sodium per <dosage unit>, equivalent to y% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium	09/10/2017	Oral, parenteral	17 mmol (391 mg) in the daily maximum dose	Talk to your doctor or pharmacist if you need <z> or more daily <dosage units> daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.	This applies only to products for which the labelled posology allows the product to be taken on a daily basis for > 1 month or repeated use for more than 2 days every week. 17 mmol (391 mg) is approximately 20% of the WHO adult recommended maximum daily dietary intake of 2 g sodium and is considered to represent 'high' sodium. This is also relevant for children, where the maximum daily intake is considered to be proportional to adults and based on energy requirements. <z doses> reflects the lowest number of dosage units for which the threshold of 17 mmol (391 mg) of sodium is reached/ exceeded. Round down to the nearest whole number. For SmPC wording please refer to PRAC recommendation: "*1.3. Sodium-containing effervescent, dispersible and soluble medicines – Cardiovascular events*" (EMA/PRAC/234960/2015)

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium laurilsulfate	09/10/2017 *Corrigendum 19/11/2018*	Cutaneous	Zero	This medicine contains x mg sodium laurilsulfate in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>. Sodium laurilsulfate may cause local skin reactions (such as stinging or burning sensation) or increase skin reactions caused by other products when applied on the same area.	The thickness of the skin varies considerably according to the body site and with age and can be an important factor in the sensitivity to sodium laurilsulfate (SLS). Sensitivity to SLS will also vary according the type of formulation (and effects of other excipients), the concentration of SLS, contact time and patient population (children, hydration level, skin color and disease). Patient populations with decreased skin barrier functions such as in atopic dermatitis are more sensitive to the irritant properties of SLS.
Sorbic acid (E 200) and salts		Topical	Zero	May cause local skin reactions, (e.g. contact dermatitis).	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sorbitol (E 420)	09/10/2017	Oral, parenteral	Zero	This medicine contains x mg sorbitol in each <dosage unit><unit volume><which is equivalent to xmg/<weight><volume>.	The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Sorbitol (E 420)	09/10/2017	Intravenous (IV)	Zero	Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects. You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.	Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary. Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be lifethreatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sorbitol (E 420)	09/10/2017	Oral, parenteral (other than IV)	5 mg/kg/day	Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.	Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
Sorbitol (E 420)	09/10/2017	Oral	140 mg/kg/day	Sorbitol may cause gastrointestinal discomfort and mild laxative effect.	
Soya oil Hydrogenated soya oil		All	Zero	<Medicinal product> contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product	In line with Arachis oil. SmPC: contraindication
Stearyl alcohol		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Sucrose		Oral	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.	SmPC proposal: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Sucrose		Oral	5g	Contains x g of sucrose per dose. This should be taken into account in patients with diabetes mellitus.	

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sucrose		Oral liquids, lozenges and chewable tablets	Zero	May be harmful to the teeth.	Information to be included only when the medicinal product may be intended for chronic use, e.g. for two weeks or more.
Sulphites including metabisulphites e.g.: Sulphur dioxide (E 220) Sodium sulphite (E 221) Sodium bisulphite (E 222) Sodium metabisulphite (E 223) Potassium metabisulphite (E 224) Potassium bisulphite (E 228)		Oral Parenteral Inhalation	Zero	May rarely cause severe hypersensitivity reactions and bronchospasm.	
Wheat starch (containing gluten)	09/10/2017 *Corrigendum 19/11/2018*	Oral	Zero	This medicine contains only very low levels of gluten (from wheat starch) <It is regarded as "gluten free">and is very unlikely to cause problems if you have coeliac disease. One <dose unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. *[* The statement 'gluten-free' applies only if the gluten content in the medicinal product is less than 20 ppm.]*	The name of the excipient on the packaging should be: 'Wheat starch'.

Name	Updated on	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Wool fat (lanolin)		Topical	Zero	May cause local skin reactions (e.g. contact dermatitis).	
Xylitol (E 967)		Oral	10 g	May have a laxative effect. Calorific value 2.4 kcal/g xylitol.	

Appendix: European Union list of fragrance allergens requiring labelling on cosmetic and detergent products

Substance	Cas No
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5
Amyl cinnamal	122-40-7
Amylcinnamyl alcohol	101-85-9
Anisyl alcohol	105-13-5
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Benzyl salicylate	118-58-1
Cinnamal	104-55-2
Cinnamyl alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
d-Limonene	5989-27-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl cinnamaldehyde	101-86-0
Hydroxycitronellal	107-75-5
Hydroxymethylpentyl-cyclohexenecarboxaldehyde	31906-04-4
Isoeugenol	97-54-1
Lilial	80-54-6
Linalool	78-70-6
Methyl heptine carbonate	111-12-6
Oak moss	90028-68-5
Tree moss	90028-67-4

Corrigendum 1 (19/11/2018)

Phenylalanine, column “Route of Administration”

Rationale: correction of an editorial mistake.

Previous version:

Phenylalanine	Oral

Corrected version:

Phenylalanine	All

Sodium laurilsulfate, column “Name”

Rationale: E number deleted for consistency with the Annex III of Regulation (EC) No 1333/2008 on food additives.

Previous version:

Sodium laurilsulfate (E 487)

Corrected version:

Sodium laurilsulfate

Wheat starch (containing gluten), columns “Information for the Package Leaflet” and “Comments”

Changes and rationale:
Column “Information for the Package Leaflet”: The wording is clarified and consistent with the food regulation (EU) No 828/2014. The statement "gluten-free" relates to the gluten content in the finished medicinal product and not in wheat starch.
Column “Comments”: The first paragraph has been deleted. According to EDQM, there is no correlation between the total protein content and the gluten content. Therefore, calculation should be based directly on the batch information about its gluten content

Previous version:

Wheat starch (containing gluten)	Wheat starch in this medicine contains only very low levels of gluten <regarded as gluten free*> and is very unlikely to cause problems if you have coeliac disease. One <dosage unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. *[* The statement “regarded as gluten-free” applies only if the gluten content in wheat starch is less than 20 ppm.]*	In compliance with the Ph. Eur. monograph, the protein limit of 0.3% in wheat starch (total protein test), means that there is no more than 100 ppm (µg/g) of gluten present in the wheat starch. The maximum level of gluten in the excipient can be calculated based on this information (protein content). *The name of the excipient on the packaging should be: “Wheat starch”.*

Corrected version:

Wheat starch (containing gluten)	Wheat starch in this medicine contains only very low levels of gluten <regarded as gluten free*> and is very unlikely to cause problems if you have coeliac disease. One <dosage unit> contains no more than x micrograms of gluten. If you have wheat allergy (different from coeliac disease) you should not take this medicine. *[* The statement "regarded as gluten-free" applies only if the gluten content in wheat starch is less than 20 ppm.]*	*The name of the excipient on the packaging should be: "Wheat starch".*

In practice,
- For products < 20 ppm the PIL should state:
"This medicine contains only very low levels of gluten (from wheat starch). It is regarded as 'gluten-free' and is very unlikely to cause problems if you have coeliac disease…."
- For products > 20 ppm the PIL should state:
"This medicine contains only very low levels of gluten (from wheat starch) and is very unlikely to cause problems if you have coeliac disease…"