# MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

## PACKAGE INSERTS FOR HUMAN MEDICINES

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

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|---|---|---|
| First publication released for comment<br>9.09 Proposed guideline on information of package inserts for human medicines (orthodox) Apr05 v1.doc – April 2005 | | April 2005 |
| Version 2 | Release for additional comment | May 2007 |
| Version 2 | Deadline for comment | 1 August 2007 |
| Version 2 | Date of Implementation | 1 August 2008 |
| Version 3 | Date of Implementation | October 2009 |
| Version 4 | Date of Implementation | With immediate effect |
| Version 5 | Implementation for new applications for registration | With immediate effect |
| | Implementation for registered products and "Old Medicines" | 02 February 2015 |

**REGISTRAR OF MEDICINES**
**MS M HELA**

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**INFORMATION FOR THE PACKAGE INSERTS FOR HUMAN MEDICINES**

## 1 PACKAGE INSERT: GENERAL NOTES

1.1 The intention of this guideline is

- to help applicants with the correct way of presenting a package insert for evaluation, and
- to enhance consistency in the content of package inserts and
- to ensure that the information included under the different headings is clear and sufficient for the proper use of the medicine while keeping in line with Regulation 9 (1) of Act 101 of 1965, as amended.

1.2 The package insert is regarded as the document that ensures the safe and effective use of the medicine under most circumstances. It presents a scientific, objective account of the medicine's use and limitation as established by the supporting evidence. The package insert should not serve the purpose of a general treatment guideline/manual of particular medical conditions.

1.3 The package insert must be approved by the Medicines Control Council (MCC) before registration can occur, and may not be changed without MCC approval after registration.

1.4 The MCC retains the discretion to require more or less detail under the respective headings, or that information is displayed in a more prominent format such as boxed and/or bolded, as it may deem necessary, while the applicant may motivate for the inclusion or exclusion of information.
MCC should give reasons in support of any changes required.
Clinical judgement regarding an individual medicine on whether to include certain information remains important.

1.5 Each section under the various headings should include only information relevant to that section. It may, however, be necessary to address some issues under more than one heading; in such instances cross-reference to the sections which contain the relevant information should be made.

1.6 When referring to properties of the active ingredient such as pharmacological or pharmacokinetic properties the approved name (INN) should be used, i.e. under the heading Pharmacological Action. When referring to properties relating specifically to the use of the medicine, the proprietary name should be used, i.e. under all other headings. Reference to the class of medicines may be referred to, when specific clinically relevant safety information is available only for the class, and then stated that it may occur with the medicine.

**Note:** The INN name "epinephrine" should be followed in brackets by "adrenaline", and the INN 'lidocaine' should be followed in brackets by 'lignocaine".

Applicants should regularly consult the list of INN names to ensure correct/updated spelling of INN names.

1.7 The package insert may not

- contain information to be seen as promotional.
- contain any comparisons with other medicines or any reference to the brand name of any medicine that is not the subject of the package insert
- contain any statements suggestive of any potential advantage over competitors.

1.8 British English language should [preferably] be used.

1.9 Measurements: For plasma concentrations the SI system should generally be used, e.g. ng/ml, mg/ml, etc. Clinical chemistry laboratory values should be expressed in SI units, e.g. mmol/litre. Blood pressure and blood gasses should be expressed as both millimetres mercury (mm Hg) and kilopascals (kPa), e.g. $pCO_2$ 34 mm Hg (4,7 kPa).

***1 Package Insert: General Notes - continued***

1.10 The word “medicine” should be used and not the word “drug”. The word drug generally indicates a substance of abuse. This does not necessarily apply to the use of concepts which include the word “drug”, e.g. drug fever, pro-drug, drug eluting stent, adverse drug reaction, non-steroidal anti-inflammatory drug.

1.11 Source references which may be allowed include:

- Goodman & Gilman’s The Pharmacological Basis for Therapeutics (Pharmacological Action.)
- Martindale: The Complete Drug Reference (For safety information only. Not for efficacy.)
- USP Dispensing Information (USP DI), as supplementary reference
- MCC monographs for ‘Old Medicines’.
- Other references or peer reviewed updated references, including information obtained from other regulatory authorities with which Council aligns itself.

1.12 Information from a Company Core Data Sheet (CCDS) will only be considered if substantiated by relevant data on which it is based.

1.13 Standard package insert information for certain medicines or categories/classes of medicines as required by Regulation 9 of the Act, or as determined from time to time by Council should also be included in the package insert, unless convincing evidence to the contrary can be provided. (Refer to the Guideline regarding standardised text for a certain medicine/class of medicine.)

1.14 For a multisource medicine (MSM) the most recently approved innovator package insert should be used as reference for the compilation of MSM package inserts. The Indications, the Dosage and Directions for Use and the safety profile for an MSM should at least be in line with that of the innovator package insert. Applicants should ensure that all safety aspects are updated in line with the latest editions of the acceptable references. Any additional information as required by the applicant should be submitted with relevant clinical data. Council reserves the right to use information from the most recently approved relevant MSM package insert.

1.15 For combination medicines, the contribution of each active ingredient should be stated where relevant.

## 2 PRESENTATION OF A PACKAGE INSERT FOR EVALUATION

A package insert presented for evaluation for a new chemical entity (NCE), for an MSM, or for a package insert amendment after registration is required to comply with the following:

2.1 A copy of the package insert–should be typed in double-spaced text in black print and should be in English (British). Colour print is not acceptable.

2.2 The spelling and grammar in the package insert text should be checked thoroughly before submission of the application. The package insert should , where relevant, be in accordance with the Trade and Metrology Act No. 77 of 1973, as amended.

2.3 The date of the proposed package insert should be included as a footer or a header, i.e. on each page. Each page should be paginated as page x of y and each text line should be numbered.

2.4 The printing quality of the package insert should be clear to enable duplication for inclusion into various documents during the evaluation and registration process.

2.5 Changes to package inserts should be indicated by underlining for additions, strike through for deletions and broken underlining for re-wording. Highlighting, track changes and colour text are not acceptable.

2.5 All statements should be adequately referenced and cross-referenced.

References for each statement should be included in a broad margin on the right hand side of each page of the package insert. Alternatively the reference numbers may be included in the text as in scientific publications.

Every statement should be verified by a reference. The exact page/s and location on the page should be stated and, if possible, the column and line number. If an entire section is quoted from one source, the reference may be listed at the end of the relevant section.

No references should, however, be included in the finalised printed package insert.

2.6 Proposed package inserts (and accompanying Patient Information Leaflets) must be presented as single-sided copies (not back-to-back).

2.7 For a package insert amendment for a medicine after registration, the approved package insert, a proposed amended package insert and the evidence/motivation for the change should be submitted together with the notification MRF4 Package Insert Amendment form. Each package insert must be accompanied by a patient information leaflet (PIL), reflecting the corresponding proposed amendments. ***[Refer also to the guideline "Package insert amendments concerning urgent safety restrictions: Urgent safety restriction notice (USRN)".]***

2.8 An electronic copy (Word document) of the package insert and the PIL should be included on an appropriate electronic storage device.

## 3 PACKAGE INSERT: CONTENT UNDER EACH HEADING

This section provides guidance on the detail which should and which should not be included under the different section headings of a package insert, as stipulated in Regulation 9 (1) of Act 101 of 1965.

In the case of a complementary medicine the following should be included:

- A statement identifying the discipline of the medicine; and
- if the medicine has not received registration with the Medicines Control Council the disclaimer "This medicine has not been evaluated by the Medicines Control Council. This medicine is not intended to diagnose, treat, cure of prevent any disease."

### 3.1 SCHEDULING STATUS

The Scheduling Status as determined by Council and published in the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended.

### 3.2 PROPRIETARY NAME AND DOSAGE FORM

The proposed proprietary name as approved by Council.

### 3.3 COMPOSITION

For the approved name the International Non-proprietary Name (INN) should preferably be used. Include, in addition to information on the active ingredient(s), as required by Regulation 9(1) of the Act, all excipients (qualitative) included in the formulation, except IPIs, including acids and bases used for pH adjustment, not present in the final product.

The quantity of the API should be stated as the quantity of the INN or INNM (INN modified), indicating the presence (not quantity) of a salt or form, where appropriate.

As per regulation 9(1) c, medicines intended for oral administration should include the warning: "contains sugar" or "sugar free", whichever is applicable. Where there is a sugar known to have intolerance or side effects, the presence of this sugar should be reflected e.g. "Contains lactose monohydrate".

## 3.4 PHARMACOLOGICAL CLASSIFICATION

In accordance with Regulation 9.1(d) and Regulation 25, the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended.

## 3.5 PHARMACOLOGICAL ACTION

In general, only mention information which is relevant to the prescriber, taking into account the approved therapeutic indication(s) and the potential adverse reactions. Statements should be brief and precise.

### 3.5.1 Pharmacodynamic properties

3.5.1.1 Describe mechanism of action (if known), pharmacodynamic effects, relevant clinical efficacy.

3.5.1.2 For antimicrobial agents:

- Do not include antimicrobial sensitivity data derived from *in vitro* testing, but include data on *in vitro* 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.

### 3.5.2 Pharmacokinetic properties

3.5.2.1 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 include reference to absorption, distribution, protein binding, biotransformation, elimination and linearity/non-linearity, as appropriate for the medicine marketed.

3.5.2.2 Include information on the intake of the medicine in relation to food intake (i.e. with or without food).

3.5.2.3 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.

3.5.2.4 Information on pharmacokinetic and pharmacodynamic relationship(s) and the contribution (if any) of metabolite(s) should be included, where relevant.

### 3.5.3 Summary of clinical studies

3.5.3.1 It may be appropriate, at the discretion of the MCC, to provide limited information of more recent clinical studies, of relevance to the prescriber.

3.5.3.2 In general, preclinical safety information is not included, but may be deemed necessary by the MCC in some situations, e.g. the relevance to pregnancy. The reason(s) for such inclusion should be provided.

## 3.6 INDICATIONS

3.6.1 The indication should be stated clearly and concisely and define the target disease distinguishing between treatment, primary prevention, secondary prevention and diagnostic indications. When appropriate it should define the target population and/or the duration of treatment (i.e. short or long term).

3.6.2 For antimicrobial agents: Indications should be linked to conditions caused by organisms known to be eradicated by the agent in the clinical data submitted. (See Pharmacological Action).

## 3.7 CONTRAINDICATIONS

3.7.1 Absolute contraindications; this 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).

3.7.2 Where the use of a medicine may be life-threatening, cause mortality or serious morbidity.

3.7.3 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 pharmacokinetics, pharmacodynamics, or common state of knowledge in medicine) for not using the combination. (Cross-reference to INTERACTIONS.)

3.7.4 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).

3.7.5 Pregnancy and/or lactation, if absolutely contraindicated. (Cross-reference to PREGNANCY AND LACTATION)

3.7.6 Hypersensitivity to any of the ingredients, including excipients.

3.7.7 Porphyria, if absolutely contraindicated. (See WARNINGS.)

## 3.8 WARNINGS and SPECIAL PRECAUTIONS

3.8.1 Specific safety issues, especially those that may lead to death or serious harm (adverse effects), may be required to be placed in a prominently displayed box and/or bolded font. Such information may be displayed at the top of this section, or may be displayed elsewhere in the package insert, where deemed appropriate.

3.8.2 Relative contraindications should appear first, followed by the other warnings.

3.8.3 Include

3.8.3.1 relative contraindications: Conditions under which use of the medicine could be acceptable, provided that special conditions for use are fulfilled.

3.8.3.2 special patient groups likely to experience medicine or class related adverse reactions under normal conditions of use, e.g. certain age groups, patients with renal or hepatic impairment or cardiac failure (include the degree of impairment), or where the incidence or severity of the reaction differs in particular populations.

3.8.3.3 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.

3.8.3.4 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.

3.8.3.5 clinically relevant interactions where, in general, the use in combination should be avoided (relative contraindication). (Cross-reference to INTERACTIONS.)

3.8.3.6 patient populations not studied in the clinical trial programme and for which there is no information available, where this is clinically relevant.

***3.8 WARNINGS and SPECIAL PRECAUTIONS - continued***

3.8.4 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'.

3.8.5 Descriptions of warnings and precautions regarding pregnancy and lactation should be addressed under the heading PREGNANCY AND LACTATION.

3.8.6 Effects on ability to drive and use machines

3.8.6.1 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.

3.8.6.2 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.

3.8.7 Porphyria: If not shown to be safe only the statement "Safety has not been established" will be allowed.

3.8.8 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.

3.8.9 Any special precaution necessary relating to excipients.

## 3.9 INTERACTIONS

3.9.1 Include information on potentially clinically relevant interactions based on the pharmacology (pharmacodynamics and/or pharmacokinetics) of the medicine, particularly on interactions which result in a recommendation regarding the use of the medicine.

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

3.9.3 Interactions referred to in other sections of the package insert should be outlined and cross-referenced to the other sections.

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

3.9.4.1 contraindication of concomitant use (cross reference to CONTRAINDICATIONS)

3.9.4.2 concomitant use not recommended (cross-reference to WARNINGS)

3.9.4.3 precautions regarding dose adjustment (cross reference to DOSAGE AND DIRECTIONS FOR USE and to WARNINGS), stating specific situations where these may be required.

For the actual dose recommendation, refer to DOSAGE AND DIRECTIONS FOR USE.

3.9.4.4 any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters

3.9.4.5 mechanism if known

3.9.4.6 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

3.9.4.7 the need for a washout period when using medicines consecutively.

***3.9 INTERACTIONS - continued***

3.9.5 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.

3.9.6 Information on other relevant interactions such as with food or pharmacologically active substances not used for medical purposes.

3.9.7 Results demonstrating an absence of interaction should only be mentioned if this is of likely major clinical interest to the prescriber.

3.9.8 Include interactions with laboratory tests and investigations.

3.9.9 If no interactions studies have been performed, this should be stated.

## 3.10 PREGNANCY AND LACTATION

### 3.10.1 Pregnancy

3.10.1.1 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.)

3.10.1.2 Recommendations on the use of the medicine at different times during pregnancy in respect of gestation.

3.10.1.3 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.

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

### 3.10.2 Women of Childbearing Potential

Recommendations on the use of the medicine in women of child-bearing potential, including contraception and testing for pregnancy, should be stated, when appropriate. It should be indicated if alternative contraception is required for patients and for their partners, during treatment and for a defined period after treatment, as appropriate. (Cross-reference to CONTRAINDICATIONS or any other section, as appropriate.)

### 3.10.3 Lactation

3.10.3.1 Information on excretion of the active substance and/or its metabolite(s) in milk. (Cross-reference to CONTRAINDICATIONS, WARNINGS or any other section, as appropriate.)

3.10.3.2 A recommendation as to whether to stop or continue breast-feeding.

### 3.10.4 Fertility

Information regarding fertility should be given in sections CONTRAINDICATIONS, WARNINGS, or SIDE EFFECTS, as appropriate.

## 3.11 DOSAGE AND DIRECTIONS FOR USE

3.11.1 Include, for each route of administration and for each indication:

3.11.1.1 dose and dose interval

3.11.1.2 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

3.11.1.3 dosage adjustment for each age category where appropriate

3.11.1.4 dosage adjustment with renal insufficiency, liver disease, dialysis, concomitant disease or interactions requiring specific dose adjustments

3.11.1.5 monitoring advice, where applicable.

3.11.1.6 cross-referencing to other sections, as relevant.

3.11.2 Where appropriate the following points should be addressed:

3.11.2.1 the maximum recommended single, daily and/or total dose

3.11.2.2 the need for dose titration

3.11.2.3 the normal duration of use and any restrictions on duration

3.11.2.4 if relevant, the need for tapering off

3.11.2.5 the intake of the medicine in relation to food intake.

3.11.3 If necessary, relevant instructions for correct administration/use, including the use of devices.

3.11.4 For parenteral preparations: Include information on compatible and incompatible solutions where this may be necessary for administration purposes.

## 3.12 SIDE EFFECTS

3.12.1. 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**.

3.12.2 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.

3.12.3 To provide clear and readily-accessed information, the section should be structured according to the following recommendations:

a) 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.

b) 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. (See annexures 1 and 2).

c) 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.

***3.12 SIDE EFFECTS - continued***

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 regulatory authorities with which Council aligns itself or may be obtained from reference sources that Council recognises, including, but not restricted to, Martindale or the USPDI. The term reporting the highest frequency should always be used and all information must be clearly referenced. The appropriateness of the source(s) remains at the discretion of Council.

  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.

- **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.

  **Note:** For a MSM package insert without its own clinical trial data, ADRs should be categorised according to the frequency classification: 'Frequent' and 'Less frequent'.

3.12.4 If there are only a few adverse reactions in total in this section, classification by SOC may be unnecessary.

3.12.5 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.

3.12.6 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.

3.12.7 Any adverse reactions resulting directly from an interaction should be included and cross-referenced to Interactions.

***3.12 SIDE EFFECTS - continued***

3.12.8 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.

3.12.9 Any adverse reaction which may be related to excipients or residues from the manufacturing process should be included.

### 3.13 KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

3.13.1 Describe acute symptoms and signs and potential sequelae of overdosage.

3.13.2 Describe recommended management of overdose e.g. symptomatic treatment, or in relation to specific agonists/antagonists or methods to increase elimination of the medicine e.g. dialysis.

### 3.14 IDENTIFICATION

As per the final product specifications

### 3.15 PRESENTATION

As per the specification for packaging

### 3.16 STORAGE INSTRUCTIONS

As per the stability information, the storage temperatures must be stated, e.g. “Store at or below X °C” or “Store between X and Y °C”. Include other relevant storage instructions such as “Keep in secondary container” where appropriate for light sensitive products.

### 3.17 REGISTRATION NUMBER

Will be allocated by Council upon registration

### 3.18 NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

### 3.19 DATE OF PUBLICATION OF THE PACKAGE INSERT

The following dates should be included:

- the date on the registration certificate of the medicine
- thereafter the date of the most recently revised package insert as approved by Council.

## 4 UPDATE HISTORY

| Date | Reason for update | Version & publication |
|---|---|---|
| April 2005 | First publication released for comment<br>9.09 Proposed guideline on information of package inserts for human medicines (orthodox) Apr05 v1.doc – April 2005 | v1 April 2005 |
| May 2007 | Release for additional comment | v2 |
| 1 August 2007 | Deadline for comment | |
| 1 August 2008 | Date of Implementation | |
| Oct 2009 | Bullets and numbering edited for easier reference;<br>Amendment of section 3.12 - Further guidance on reporting of Side-effects 3.12.1.3 c) Frequency of ADRs | v3 October 2009 |
| June – Dec 2012 | Amendments to sections: 1.4, 1.6, 1.7, 2.7, 3.2, 3.5.2.1, 3.5.2.2, 3.7.5, 3.7.7, 3.8.2, 3.8.3.1, 3.8.3.2, 3.8.3.5, 3.11.2.5, 3.12.1.3 (a), 3.12.1.5, 3.12.1.8, 3.12.1.9, 3.12.3.2, 3.14, 3.15, 3.16, 3.17, 3.19.<br>Additions to sections: 1.6, 1.10, 1.12, 1.13, 1.14, 1.15, 2.2, 2.3, 2.5, 2.6, 3.1, 3.3, 3.4, 3.8.3.4, 3.8.5, 3.8.6, 3.9.5, 3.9.8, 3.9.9, 3.10.2, 3.12.1.3 (c).<br>Deletions of text in sections: 1.8, 1.11, 1.13, 1.14, 1.15, 3.8.3.6, 3.8.5, 3.12.1.1, 3.12.1.2, 3.12.1.3 (c). | v4 December 2012 |
| Dec 2012 | Date of implementation | |
| Dec 2013 | Amendment of sections 3, 3.8 and 3.12 in line with the amended regulations published on 15 November 2013, to combine the section Warnings and Special Precautions. Addition of information on CAMs | v5 January 2014 |
| With immediate effect | Implementation for new applications for registration | |
| 02 February 2015 | Implementation for registered products and “Old Medicines” | |

**Annexure 1**

**SYSTEM ORGAN CLASS (SOC) LIST: THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES TERMINOLOGY (MedDRA)**

*INTERNATIONALLY AGREED ORDER*

- Infections and Infestations
- Neoplasms benign and malignant (including cysts and polyps)
- Blood and the lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Nervous system disorders
- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders
- Hepato-biliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal, connective tissue and bone disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital and familial/genetic disorders
- General disorders and administrative site conditions
- Investigations
- Injury and poisoning
- Surgical and medical procedures
- Social circumstances

**Annexure 2**

**SYSTEM ORGAN CLASS (SOC) LIST:**
**THE WORLD HEALTH ORGANISATION ADVERSE REACTION TERMINOLOGY (WHOART)**

- Skin and appendages disorders
- Musculoskeletal system disorders
- Collagen disorders
- Central & peripheral nervous system disorders
- Autonomic nervous system disorders
- Vision disorders
- Hearing and vestibular disorders
- Special senses other, disorders
- Psychiatric disorders
- Gastro-intestinal disorders
- Liver and biliary system disorders
- Metabolic and nutritional disorders
- Endocrine disorders
- Cardiovascular disorders, general
- Myo-, endo-, pericardial & valve disorders
- Heart rate and rhythm disorders
- Vascular (extracardiac) disorders
- Respiratory system disorders
- Red blood cell disorders
- White cell and RES disorders
- Platelet, bleeding & clotting disorders
- Urinary system disorders
- Reproductive disorders, male
- Reproductive disorders, female
- Foetal disorders
- Neonatal and infancy disorders
- Neoplasms
- Body as a whole – general disorders
- Application site disorders
- Resistance mechanism disorders
- Secondary terms – events
- Poison specific terms