The GCC Guidance for Presenting the SPC, PIL and Labeling Information

Version 2.0

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## Document Control

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<td>30/01/2010</td>
<td>Executive Directorate of Product Evaluation and Standards Setting</td>
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</tr>
<tr>
<td>1.1</td>
<td>17/05/2011</td>
<td>Executive Directorate of Product Evaluation and Standards Setting</td>
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<td>22/12/2013</td>
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Note: For most recent update please refer to annex 1.
I. Introduction

These guidelines are adapted from the EMA *Notice to applicants and regulatory guidelines medicinal products for human use, EudraLex - Volume 2.*

This document is indented to guide applicants on how to present the required information by the Gulf Cooperation Council (GCC) States for:

- Summary of Product Characteristics (SPC);
- Patient Information Leaflet (PIL); and
- Labeling.

The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively. The Patient Information Leaflet (PIL) shall be drawn up in accordance with the SPC.

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

When submitting a new application for registration, renewal or variation, the information presented by the applicant regarding the SPC, PIL and labeling must follow this guidance. Additionally, it should be noted that pharmaceutical products with different strengths must have different packaging color codes that differentiate between different strengths. Furthermore, the applicant must provide Arabic translation of the information on the outer package including: name of the medicinal product along with storage conditions for all medicines except those used solely in hospitals.

Following the GCC’s approval of the SPC, PIL and labeling contents, such contents cannot be changed except with the approval of the GCC (*refer to guidelines for variation requirements*).
II. Labeling

The data should be presented according to the template below, irrespectively of their sequence on the actual labeling and their position and possible repetition on the individual sides/flaps of the packaging (e.g. top flap, front, back etc.).

A separate text for outer and inner packaging labeling should be completed per strength and per pharmaceutical form.

Bracketing convention:

{text}: Information to be filled in.

<text>: Text to be selected or deleted as appropriate.

1. Particulars to appear on the <outer packaging> <and> <the immediate packaging>

a. Name of the medicinal product

   {(Invented) name strength pharmaceutical form}

   {Active substance(s)}

   - A standard packaging box has six faces on which information can be displayed. If it is feasible, display a product description on more than three non opposing faces.

   - Use blank space to emphasize critical information such as the medicine name, generic name and strength.

   • Note: The invented (trade) name in Arabic language should be added.

b. Statement of active substance(s)

   - Expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight. Where the active substance is present as a salt, this should be clearly indicated.
c. List of excipients

- *Express qualitatively those excipients known to have a recognised action or effect. However, if the medicinal product is a parenteral, a topical or an eye preparation or if used for inhalation, all excipients must be stated.*

d. Pharmaceutical form and contents

- *Contents by weight, by volume or by number of doses or number of units of administration of the medicinal product (e.g. 28 tablets, 100 mL, ...)*

For injectable medicine:

a. The strength of injectable medicines should be express in quantity /unite volume (mg/ml) e.g. : 5mg/ml

b. Include a representation of the full volume strength , e.g. : total quantity in total volume (mg/ml) (25 mg/5ml). This should be emphasized for single-dose containers.

c. Display concentration in total quantity/total volume e.g.( 200 mg/10ml ), even if other units of concentration such as percentage and ratios are present e.g. (: 2 % ) (20 mg/ml).

e. Method and route(s) of administration

- *Method of administration: directions for proper use of the medicinal product, use positive statements if possible - use “DO” rather than “DO NOT” ,e.g. if the drug given for intravenous , use : (For intravenous infusion) , rather than (NOT for I.M) e.g. “Do not swallow”, “Do not chew”,(should be deleted) “Shake well before use”. In all cases, and especially if full details cannot be included on the outer packaging itself, a reference to the patient information leaflet must be made:*

- Read the patient information leaflet before use.

f. Special warning that the medicinal product must be stored out of the reach and sight of children

- *Keep out of the reach and sight of children.*

g. Other special warning(s), if necessary
h. Manufacturing and Expiry dates

- Dates should be expressed with the month given as 2 digits or 3 characters and the year as 4 digits. e.g.: 02/2010, Feb 2010.

- Where applicable, the shelf life after reconstitution, dilution or after first opening the container should be included.

i. Special storage conditions

   [For recommended labeling statements see Appendix 1]

   - Note: Storage conditions in Arabic language should be added.

j. Special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate

   [E.g. radiopharmaceuticals, cytostatics.]

   [A reference to any appropriate collection system in place should be included on the outer packaging.]

k. Manufacturer name

l. Marketing company

m. Name and address of the marketing authorisation holder

   {Name and Address}

   <{tel}>

   <{fax}>

   <{e-mail}>

n. Marketing authorisation number(s)

o. Batch number

   <Batch> <Lot> <BN> {number}

p. General classification for supply
<Medicinal product subject to medical prescription.>

<Medicinal product not subject to medical prescription.>

q. Price

2. Minimum particulars to appear on blisters or strips

a. Name of the medicinal product

{(Invented) name strength pharmaceutical form}

{Active substance(s)}

- The name and strength of the product should be appear over each blister pocket, if the size of the pockets is too small, the information should be repeated in a pattern across the entire strip.

b. Name of the marketing authorisation holder

{Name}

c. Manufacturing and Expiry dates

- Dates should be expressed with the month given as 2 digits or 3 characters and the year as 4 digits. e.g.: 02/2010, Feb 2010.

d. Batch number

.BatchNorm. <Lot> <BN> {number}

- Batch number and Expiry date should be at the end of each blister strip, if technically possible this could be applied to both ends.

e. Other

[Space permitting, any other information necessary for the correct use and administration of the product can be included here, e.g. calendar days.]
3. Minimum particulars to appear on small immediate packaging units

Small immediate packaging units are defined as containers sized up to and including 10 ml. On a case-by-case basis the minimum particulars could also be considered for other containers where it is not be feasible to include all the information. Such exceptional cases have to be justified, discussed and agreed upon with the GCC.

a. Name of the medicinal product and route(s) of administration

{(Invented) name strength pharmaceutical form}

{Active substance(s)}

{Route of administration}

b. Method of administration

- Method of administration: directions for proper use of the medicinal product, use positive statements if possible - use “DO” rather than “DO NOT”, e.g. if the drug given for intravenous use: (For intravenous infusion), rather than (NOT for I.M) e.g. “Do not swallow”, “Do not chew”, (should be deleted) “Shake well before use”. If full details cannot be included on the immediate packaging itself, a reference to the patient information leaflet should be made, e.g. “Read the patient information leaflet before use”.

c. Manufacturing and Expiry dates

- Dates should be expressed with the month given as 2 digits or 3 characters and the year as 4 digits. e.g.: 02/2010, Feb 2010.

- Where applicable, the shelf life after reconstitution, dilution or after first opening the container should be included.

d. Batch number

<br> <Lot> <BN> {number}. 
e. Contents by weight, by volume or by unit

For injectable medicine:

a. The strength of injectable medicines should be express in quantity/unit volume (mg/ml) e.g. : 5mg/ml.

b. Include a representation of the full volume strength, e.g. : total quantity in total volume (mg/ml) (25 mg/5ml). This should be emphasized for single-dose containers.

c. Display concentration in total quantity/total volume e.g.( 200 mg/10ml), even if other units of concentration such as percentage and rations are present e.g. (: 2 % ) (20 mg/ml).

f. Special storage conditions

[For recommended labeling statements see Appendix 1]

- If drug requires refrigeration, highlight storage conditions.

- Use positive statements to give directions.

g. Other

- Space permitting, any other information necessary for the correct use and administration of the product can be included here.
III. Patient Information Leaflet (PIL)

A separate patient information leaflet should be provided per strength and per pharmaceutical form in cases of different indications for different strengths and/or dosage forms. However, applicants may present patient information leaflets for different strengths in one document during the evaluation process, clearly indicating the strength or presentation to which alternative text elements refer. Where applicants consider to also market a combined package leaflet, a detailed justification for such a combined patient information leaflet should be provided in the application at submission. E.g. (Different strengths have the same indication).

The following items must appear in the patient information leaflet as required by this guidance. In exceptional cases, alternative headings may be acceptable, especially for those headings containing <take><use> or where a different wording would be more appropriate for the product concerned e.g. to better reflect the user of the product. This should not in any case impact on the content required for the section concerned. Applicants should justify the use of alternative headings (e.g. by reference to user testing results). For certain medicinal products not all items may be relevant, in this case the corresponding heading should not be included.

It is important that the PIL can easily be tracked for updates and review. Each PIL should be given a reference number along with the date the leaflet was issued and a suitable review date. Each PIL should be reviewed every 3 years or when necessary.

Bracketing convention:

{text}: Information to be filled in.

<text>: Text to be selected or deleted as appropriate.
Patient Information Leaflet (PIL)

{(Invented) name strength pharmaceutical form}

{Active substance(s)}

The (invented) name of the medicinal product (referred to as X throughout this document) followed by the strength and pharmaceutical form (i.e. as it appears in the SPC) should be stated here in bold. This should be followed by the active substance(s) (as stated on the label section 1), which may be written on the line below.

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

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your <doctor, health care provider> <or> <pharmacist>.

- <This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.>

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

In this leaflet:

1. Serious side effects
2. What {product name} is and what it is used for
3. Before you <take> <use> {product name}
4. How to <take> <use> {product name}
5. Possible side effects
6. How to store {product name}
7. Further information
1. Serious side effects

- This section should include serious and major side effects as consistent with the black box warning in the SPC if applicable. Also, A black Box Warning might be added if requested by the National Pharmacovigilance and Drug Safety Center (NPC).

2. What {product name} is and what it is used for

- Pharmacotherapeutic group:

The pharmacotherapeutic group or type of activity should be stated here using patient understandable language.

- Therapeutic indications:

The therapeutic indications should be stated here, using patient understandable language. If appropriate, specify that:

<This medicine is for diagnostic use only.>

3. Before you <take> <use> {product name}

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

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

b. Take special care with {product name}

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

c. <Taking> <Using> other medicines, herbal or dietary supplements

- Describe the effects of other products on {product name} and vice versa.
<Please tell your <doctor, health care provider> <or> <pharmacist> if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.>

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

- Interactions not related to medicinal products should be mentioned here. Where relevant, guidance should always be included to clarify if the medicine must be taken with food, during/before meals, or clearly state if food/meals have no influence, etc.

e. Pregnancy and breast-feeding

- Where the information is significantly different, pregnancy and breast-feeding information can be presented under separate headings.

- Include conclusion summary of the information given in the SPC, in addition to the following optional statement:

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

f. Driving and using machines

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

- <Do not use any tools or machines.>

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

- If appropriate, details of those excipients knowledge of which is important for the safe and effective use of the medicinal product, including relevant warnings for residues from the manufacturing process.

4. How to <take> <use> {product name}

<Always <take> <use> {product name} exactly as your doctor or health care provider has told you. You should check with your <doctor, health care provider> <or> <pharmacist> if you are not sure.> <The usual dose is...>
— You may include the following sub-headings within the headings given below if needed to increase readability:

- Instructions for proper use
- Dosage
- Method and/or route(s) of administration
- Frequency of administration
- Duration of treatment

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

- Describe how to recognise if someone has taken an overdose and what to do.

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

- Make clear to patients what they should do after irregular use of a product; e.g.

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

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

- Indicate any effects of interrupting or ending the treatment early, if applicable.
- Indicate withdrawal effects when the treatment ends, when necessary.
- As appropriate, close this section with:

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

5. Possible side effects

— Describe the side effects and whenever possible, an estimate of frequency should be provided, expressed in standard category of frequency (see Appendix 2).

— Begin this section with: "Like all medicines, {product name} can cause side effects, although not everybody gets them".
- Describe, if necessary, the actions to be taken. If the patient needs to seek help urgently, the use of the term <immediately> is recommended; for less urgent conditions, <as soon as possible> can be used.

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

6. How to store {product name}

- Keep out of the reach and sight of children.

- <Do not store above °C>, <Store in the original <container><carton>>

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

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

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

7. Further information

a. What {product name} contains

- The active substance(s) (expressed qualitatively and quantitatively) and the other ingredients (expressed qualitatively) should be identified.

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

b. What {product name} looks like and contents of the pack
– The pharmaceutical form should be stated.

– It is recommended to include a physical description e.g. shape, color, texture, imprint.

– All pack sizes for this pharmaceutical form and strength should be detailed here; if appropriate indicate that not all pack sizes may be marketed. A cross-reference to other pharmaceutical forms and strengths may be included.

c. Marketing Authorisation Holder and Manufacturer

{Name and address}

{tel}

{fax}

{e-mail}

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

{Name}

{Address} {City}

Tel: + {telephone number}

{e-mail}

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

d. This leaflet was last approved in {MM/YYYY}; version number {   }

e. To report any side effect(s):

- **Saudi Arabia:**

  – The National Pharmacovigilance and Drug Safety Centre (NPC)
    - Fax: +966-11-205-7662
    - Toll free phone: 8002490000
    - E-mail: npc.drug@sfda.gov.sa
    - Website: www.sfda.gov.sa/npc

- **Other GCC States:**

  – Please contact the relevant competent authority.
f. Council of Arab Health Ministers

The following statements issued by the Council of Arab Health Ministers should be printed in the PIL.

<table>
<thead>
<tr>
<th>This is a Medicament</th>
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<tr>
<td>– Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.</td>
</tr>
<tr>
<td>– Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.</td>
</tr>
<tr>
<td>– The doctor and the pharmacist are the experts in medicines, their benefits and risks.</td>
</tr>
<tr>
<td>– Do not by yourself interrupt the period of treatment prescribed for you.</td>
</tr>
<tr>
<td>– Do not repeat the same prescription without consulting your doctor.</td>
</tr>
<tr>
<td>– Keep all medicaments out of reach of children.</td>
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</tbody>
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Council of Arab Health Ministers

Union of Arab Pharmacists

g. This patient information leaflet is approved by the Saudi Food and Drug Authority
IV. Summary of Product Characteristics (SPC)

During the evaluation process, applicants may present SPCs for different strengths in one document, clearly indicating with grey-shaded titles the strength or presentation to which alternative text elements refer. However, a separate SPC per strength and per pharmaceutical form, containing all pack-sizes related to the strength and pharmaceutical form concerned will have to be provided by the applicant.

ADD: Black Box Warning if applicable.

A black box warning is designed to call attention to serious or life threatening risks. This section can be adapted from the US FDA professional product information leaflet.

Bracketing convention:

{text}: Information to be filled in.

<text>: Text to be selected or deleted as appropriate.

1. Name of the medicinal product

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

(Invented) name strength pharmaceutical form

2. Qualitative and quantitative composition

- Full details of the qualitative and quantitative composition in terms of the active substance(s) and excipients.

- A standard statement should be included at the end of the section, i.e. ‘For a full list of excipients, see section 6.1.

3. Pharmaceutical form

- Full description of the pharmaceutical form should be provided.
– It is recommended that a visual description of the appearance of the product (color, markings, etc.) is given, including information on pH and osmolarity as required e.g.:

‘Tablet White, circular flat bevelled-edge tablets marked ‘100’ on one side’.

– In case of tablets designed with a score line, information should be given whether or not reproducible dividing of the tablets has been shown. e.g.:

<The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.>

<The tablet can be divided into equal halves.>.

4. Clinical particulars

4.1 Therapeutic indications

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

– When the product is indicated in a specific age group such as children/adolescents, the indication should state the age limit e.g. ‘X is indicated in <children> <adolescents> from the age of X <months><years >’.

4.2 Posology and method of administration

– In case of restricted medical prescription start this section by specifying the conditions.

– The route of administration and concise relevant instruction for correct administration and use should be given here.

– Instructions for preparation are to be placed under section 6.6 or 12, and cross-referenced here.
- Dose recommendations (e.g. mg, mg/kg, mg/m²) should be specified per dose interval for each category where appropriate (specify age/weight/body surface area of subsets of the population as appropriate). Frequency of dosing should be expressed using time units (e.g. once or twice daily or every 6 hour) and, to avoid confusion, abbreviations e.g. OD or BID should not be used.

Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the need for dose titration,
- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation,
- advice on action to be taken if one or more dose(s) is (are) missed, or e.g. in case of vomiting (the advice should be as specific as possible, taking into consideration the recommended frequency of dosing and relevant pharmacokinetic data)
- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetics),
- the intake of the product in relation to drink and food intake, e.g. with alcohol, grapefruit or milk,
- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate,
- interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SPC and
- it may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose-titration.

- Dosage adjustments or other posology related information on special populations should be presented here, in well-defined sub-sections ordered by importance, e.g. regarding: elderly population; paediatric population; renal impairment; hepatic impairment,
patients with a particular genotype; other relevant special population (e.g. patients with other concomitant disease or overweight patients).

4.3 Contraindications

– Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include a particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, a particular genotype and prior adverse reactions to the medicine or class of medicines). The situations should be unambiguously, comprehensively and clearly outlined. Only if pregnancy or breastfeeding is contraindicated, should it be mentioned here. Hypersensitivity to the active substance or to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients.

4.4 Special warnings and precautions for use

– The order of warnings and precautions should be determined by the importance of the safety information provided.

4.5 Interaction with other medicinal products and other forms of interaction

– This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product.

– The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product.
– **Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk. Patient groups in which use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not to be repeated here.**

– **The following should be described:**

  o The conditions, in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled. In particular, specific risk minimisation measures requested as part of a Risk Management Plan to ensure safe and effective use should be described in this section. (*For example:* “Liver function should be monitored before initiation of treatment and monthly thereafter”, “Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation”, “Women of childbearing potential should use contraception”, …)

  o Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions (usually serious or common), e.g. elderly, children, patients with renal or hepatic impairment (including the degree of impairment, e.g. mild, moderate or severe), patients having an anaesthetic or patients with cardiac failure (including in this case the NYHA Classification for example). Cross-reference to section 4.8 on the differential effects in terms of frequency and severity of the specified adverse reaction should be provided.

  o Serious adverse reactions to which healthcare professionals need to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.

  o If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.

  o Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there
is a need for awareness of symptoms or signs representing early warning of a serious adverse reaction, a statement should be included.

- Any need for specific clinical or laboratory monitoring should be stated. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice. If dose reduction or other posology is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

- Any warnings necessary for excipients or residues from the manufacturing process.

- For herbal preparations containing alcohol, information about the ethanol content in the medicinal product should be included in accordance with the Guideline on excipients in the label and package leaflet of medicinal products for human use.

- Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known.

- Any particular risk associated with an incorrect route of administration (e.g. necrosis risk with extravasation of intravenous formulation, or neurological consequences of intravenous use instead of intramuscular use), should be presented, with advice on management if possible.

- In exceptional cases, especially important safety information may be included in bold type within a box.

- Any adverse reactions described in this section or known to result from conditions mentioned here should also be included in section 4.8.
Specific interference with laboratory tests should be mentioned when appropriate, e.g. Coombs test and Beta-lactams. They should be clearly identified with a subheading, e.g. “Interference with serological testing”.

In general, descriptions of warnings and precautions regarding pregnancy and breastfeeding, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and 4.5, respectively. However in specific cases of major clinical importance it might be more appropriate to describe specific precautionary measures in this section, e.g. contraception measures, or when concomitant use of another medicine is not recommended, and with cross reference to section 4.5, 4.6, or 4.7.

Paediatric population:

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

If no interaction studies have been performed, this should be clearly stated.

<No interaction studies have been performed.>

<Interaction studies have only been performed in adults.>

4.6 Fertility, Pregnancy and lactation

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

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

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

- The following should be mentioned:
  - Women of childbearing potential / Contraception in males and females.
  - Pregnancy
  - Breastfeeding
  - Fertility

- [For Pregnancy and lactation statements see Appendices 3 & 4 ]

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 addressing the performance related to driving or using machines, specify whether the medicinal product has:
  - a. no or negligible influence;
  - b. minor or moderate influence, or
  - c. major influence on these abilities.

Effects of the disease itself on these abilities should not be discussed.

<(Invented name) has <no < or negligible> influence> <minor or moderate influence> <major influence> on the ability to drive and use machines.>
No studies on the effects on the ability to drive and use machines have been performed.

Not relevant.

4.8 Undesirable effects

- This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC.

- The content of this section should be justified in the Clinical Overview of the marketing authorization application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product. In addition, the whole section could be revised at the renewal of the marketing authorization, where the safety profile of most products is likely to be well established, and thereafter at each of the three-yearly PSUR.

- It is important that the whole section is worded in concise and specific language and does not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability such as “well tolerated”, “adverse reactions are normally rare”, etc. Statements on lack of proof of causal association should not be included.
In order to provide clear and readily accessible information, section 4.8 should be structured according to the following recommendations:

a. Summary of the safety profile

b. Tabulated summary of adverse reactions

c. Description of selected adverse reactions

d. <Paediatric population>

e. <Other special population(s)>

To report any side effect(s):

- **Saudi Arabia:**
  - The National Pharmacovigilance and Drug Safety Centre (NPC)
    - Fax: +966-11-205-7662
    - Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2334-2340.
    - Toll free phone: 8002490000
    - E-mail: npc.drug@sfda.gov.sa
    - Website: www.sfda.gov.sa/npc

- **Other GCC States:**
  - Please contact the relevant competent authority.

**a. Summary of the safety profile**

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

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

An example of an acceptable statement is given below:

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

b. Tabulated list of adverse reactions

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

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

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

The table should be presented according to the MedDRA system organ classification. The system organ class (SOC) should be presented in the order shown in the annex. Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any adverse reactions should be assigned to the most relevant SOC related to the target organ. For example, PT ‘Liver function test abnormal’ should be assigned to the SOC ‘Hepatobiliary disorders’ rather than to the SOC ‘Investigations’.

Within each system organ class, the adverse reactions should be ranked under headings of frequency, most frequent reactions first. Within each frequency grouping, adverse reactions
should be presented in the order of decreasing seriousness. The names used to describe each of
the frequency groupings should follow standard terms established in each official language using
the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon
(≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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

Where additional details about an adverse reaction are described in section c), the reaction
concerned should be highlighted, for example with an asterisk, and, “see section c)” should be
included as a footnote.

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

c. Description of selected adverse reactions

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

This section should include information characterising individual serious and/or frequently
occurring adverse reactions, or those where there have been reports of particularly severe cases.
The information should provide frequency and may describe for example reversibility, time of
onset, severity, duration, mechanism of the reaction (if of clinical relevance), dose relationship,
relationship with duration of exposure or risk factors. Measures to be taken to avoid specific
adverse reactions or actions to be taken if specific reactions occur should be mentioned under
section 4.4 and cross-referenced here.

Information on the occurrence of withdrawal reactions may be mentioned here with cross-
reference to section 4.2 in case of need for tapering off or advice on discontinuation of the
product. Mention should be made here of any differences between different dosage forms in respect of adverse reactions.

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

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

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

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

d. <Paediatric population>

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

The extent and age characteristics of the safety database in children should be described (e.g. from clinical trials or pharmacovigilance data). Uncertainties due to limited experience should be stated. If the observed safety profile is similar in children and adults this could be stated: e.g. “Frequency, type and severity of adverse reactions in children are <expected> to be the same as in adults”. Similarly, it is appropriate to state whether the safety profiles in the different paediatric subsets are similar or not.

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and paediatric populations, or in any relevant age groups, should be described and presented by age group. If there is a need for specific monitoring, this should be highlighted by cross-referencing to section 4.4. For clinically relevant differences, a separate table listing such adverse reactions by frequency can be added and presented by relevant age groups if appropriate. If some paediatric adverse reactions are considered common (≥1/100 to <1/10) or very common (≥1/10), the frequencies should be
provided in parentheses. In case of major difference with the safety profile in adults, a summary of the safety profile in children could be presented to facilitate the presentation of the information. Available information, from any source scientifically validated, on long-term safety in children (e.g. on growth, mental development and sexual maturation) should also be summarised, whether positive or negative, with cross-reference to section 5.1 if appropriate. Any risk factors such as duration of treatment or period at risk should be specified.

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

e. <Other special populations>

This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, patients with other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate.

Adverse reactions may also be related to genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials.

4.9 Overdose

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

- *Taking into account all relevant evidence, describe management of overdose in man, e.g. in relation to monitoring or use of specific agonists/antagonists, antidotes or methods to increase elimination of the medicinal product such as dialysis.*
5. Pharmacological properties

5.1 Pharmacodynamic properties

Describe the following:

- Pharmacotherapeutic group: {group}, ATC code: {code}. If an ATC code is not yet available, this should be mentioned as ‘not yet assigned’.
- Mechanism of action (if known).
- Pharmacodynamic effects.
- Clinical efficacy and safety.

5.2 Pharmacokinetic properties

- Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.
- Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.
- Pharmacokinetics items, which could be included in this section when relevant, are given below.
  
  a. General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility etc.

  b. General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.

  - Absorption: complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; $T_{\text{max}}$; the influence of food; in case of locally applied medicinal product the systemic bioavailability.
  
  - Distribution: plasma protein binding; volume of distribution; tissue and/or plasma concentrations; pronounced multi-compartment behavior.
• **Biotransformation:** degree of metabolism; which metabolites; activity of metabolites; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.

• **Elimination:** elimination half-lives, the total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites.

• **Linearity/non-linearity:** linearity/non-linearity of the pharmacokinetics of the new compound with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.

  Additional relevant information should be included here.

  a. **Characteristics in patients**

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

  b. **Pharmacokinetic/pharmacodynamic relationship(s)**

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

    • Contribution (if any) of metabolite(s) to the effect.

5.3 Preclinical safety data

  - The findings of the non-clinical testing should be described in brief and qualitative statements as outlined in the following example statements:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.>

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Conclusions on the environmental risk assessment on the product should be included where relevant, with reference to section 6.6.

6. Pharmaceutical particulars

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks.

Each to be listed on a separate line according to the different parts of the product.

6.2 Incompatibilities

Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated.

Statements concerning compatibility of the product with other medicinal products or devices should not be included in this section but in section 6.6. Statements concerning pharmacological incompatibilities with food should be included in section 4.5.

If appropriate, the standard statement, ‘Not applicable’, should be included.

For certain pharmaceutical forms, e.g. parenterals, either of the following standard statements should be included as appropriate:
<In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.>

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

6.3 Shelf life

- Information on the finished product shelf life and on the in-use stability after 1st opening and/or reconstitution/dilution should appear here. Only one overall shelf life for the finished product is to be given even if different components of the product may have a different shelf life (e.g. powder & solvent).

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

6.4 Special precautions for storage

- General storage conditions of the finished product should appear here, together with a cross-reference to section 6.3 where appropriate:

<For storage conditions of the <reconstituted> <diluted> medicinal product, see section 6.3.>

- [For recommended labeling statements see Appendix 1]

6.5 Nature and contents of container

- The material of construction of the immediate container should be stated (‘Type I glass vials’, ‘PVC/Aluminium blisters’, ‘HDPE bottles’); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, inhaler devices, desiccant. The container of any solvent provided with the medicinal product should also be described. Excessive detail, e.g., concerning the color of the stopper, the nature of the heat-seal lacquer, should usually not be included. Examples on the text in this section:

‘<Volume> ml suspension in a pre-filled syringe (type I glass) with plunger stopper (chlorobutyl rubber) with or without needle in pack sizes of 5 or 10.’
‘HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack-sizes of 30, 60 or 90 filmcoated tablets.’

- All pack sizes must be listed. Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If applicable, add:
  
  <Not all pack sizes may be marketed.>

6.6 Special precautions for disposal <and other handling>

- Include practical instructions for preparation and handling of the product, where applicable, including disposal of the medicinal product, and waste materials derived from the used medicinal product.

- If applicable, e.g. for cytotoxics, the following standard statement should be included, ‘Any unused product or waste material should be disposed of in accordance with local requirements.’

- If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the following standard statement should be included:

  <No special requirements.>

7. Marketing authorisation holder

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>
8. Marketing authorisation number(s)

9. Date of first Authorisation/ renewal of the authorisation

<DD/MM/YYYY> <DD month YYYY>

10. Date of revision of the text

{MM/YYYY}

11. <Dosimetry>

- For radiopharmaceuticals, full details of internal radiation dosimetry.

12. <Instructions for preparation of radiopharmaceuticals>

- Any unused product or waste material should be disposed of in accordance with local requirements.

- For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform to its specifications.
Appendix 1: Recommended labeling statements

- The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table 1.

Table 1: Recommended labeling statements for finished pharmaceutical products (FPPs)

<table>
<thead>
<tr>
<th>Testing condition under which the stability of the FPP has been demonstrated</th>
<th>Recommended labeling statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 °C/65% RH (long-term)</td>
<td>“Do not store above 30 °C”*</td>
</tr>
<tr>
<td>40 °C/75% RH (accelerated)</td>
<td></td>
</tr>
<tr>
<td>5 °C ± 3 °C</td>
<td>”Store in a refrigerator (2 °C to 8 °C)”</td>
</tr>
<tr>
<td>-20 °C ± 5 °C</td>
<td>“Store in freezer”</td>
</tr>
</tbody>
</table>

* “Protect from moisture” should be added as applicable.

- Additional labeling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table 2.

Table 2: Additional labeling statements for use where the result of the stability testing demonstrates limiting factors

<table>
<thead>
<tr>
<th>Limiting factors</th>
<th>Additional labeling statements, where relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPPs that cannot tolerate refrigeration</td>
<td>&quot;Do not refrigerate or freeze&quot;</td>
</tr>
<tr>
<td>FPPs that cannot tolerate freezing</td>
<td>&quot;Do not freeze&quot;</td>
</tr>
<tr>
<td>Light-sensitive FPPs</td>
<td>&quot;Protect from light&quot;</td>
</tr>
<tr>
<td>FPPs that cannot tolerate excessive heat, e.g. suppositories</td>
<td>“Store and transport not above 30 °C”</td>
</tr>
<tr>
<td>Hygroscopic FPPs</td>
<td>“Store in dry condition”</td>
</tr>
</tbody>
</table>
Appendix 2: Frequency of adverse drug reactions

- The following standard categories of frequency are recommended:

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>&gt; 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>&gt; 1/100 and &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>&gt; 1/1000 and &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>&gt; 1/10,000 and &lt; 1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000</td>
</tr>
</tbody>
</table>
Appendix 3: Pregnancy statements

I. Pregnancy Categorization:

1. Pregnancy Category A:

For pregnancy category A, if adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of a risk in later trimesters.

The labeling must state:

“Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first {second, third, or all} trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed.

If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state:

Reproduction studies have been performed in {kinds of animal(s)} at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to {name of drug}”.

1. معامل الحمل فئة A:

يُعرف معامل الحمل للدواء بالحرف A إذا تولفت دراسات كافية وموثوقة إحصائيا في المرأة الحامل ولم تظهر أي خطر على الجنين في الثالث الأول من الحمل وكذلك لم يلاحظ فيها أي دلالة للخطر على الجنين في المراحل الأخرى من الحمل.

صيغة كتابة معامل الحمل فئة A في النشرة الدوائية:

يمكن أن يكون النص في النشرة كالآتي:

“معامل الحمل للدواء [اسم الدواء] هو A، حيث لم تظهر الدراسات في المرأة الحامل أن الدواء [اسم الدواء] يزيد من الخطر على الجنين في مراحل الحمل الثلاثة إذا استعمل خلال فترة الحمل. و حيث أن الدراسات المنتاحة لـ
2. **Pregnancy Category B:**

For pregnancy category B, if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

**The labeling must state:**

“**Reproduction studies have been performed in {kind(s) of animal(s)} at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to {name of drug}. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.”

If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), **the labeling must state:**

“**Pregnancy Category B. Reproduction studies in {kind(s) of animal(s)} have shown {describe findings} at (x) times the human dose. Studies in pregnant women, however, have not shown that {name of drug increases the risk of abnormalities when administered during the first {second, third, or all} trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, {name of drug} should be used during pregnancy only if clearly needed”**.
2. Pregnancy Category C:

There are two conditions for pregnancy category C:

1- For pregnancy category C, if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

B. معامل الحمل فئة B

يُعرف معامل الحمل فئة B بأنه إذا كانت الدراسات الكافية والموزونة على الحيوان لم تظهر أي ضرر على الجنين، وكذلك عدم توفر دراسات كافية وموزونة في النساء الحوامل.

صيغة كتابة معامل الحمل فئة B في النشرة الدوائية:

"معامل الحمل للدواء [اسم الدواء] هو B حيث أظهرت دراسات التناسل والتي تم إجراؤها على الحيوان إنوع الحيوان / بجرعات تعادل [مقدار الجرعة] من الجرعة المستخدمة في الإنسان عدم وجود أي دليل على قصور في الخصوبة أو ضرر على الجنين بسبب الدواء [اسم الدواء]، ومع ذلك، لا توجد دراسات كافية وموزونة في النساء الحوامل. وحيث أن دراسات التناسل في الحيوان لا تطبق تماما على الإنسان، فيجب عدم استعمال هذا الدواء إلا في حالة الاتجاه الواضح والضروري له.

في حال أظهرت دراسات التناسل في الحيوان وجود أثار جانبية (غير انخفاض في معدل الإخصاب)، ولكن الدراسات الكافية والموزونة التي تم إجراؤها على النساء الحوامل فشلت في إثبات وجود مخاطر على الجنين خلال الثالث الأول من الحمل وكذلك ليس هناك دليل على وجود مخاطر في باقي فترات الحمل، فتتى ذكر العبارة التالية في النشرة الداخلية:


3. Pregnancy Category C:

There are two conditions for pregnancy category C:

1- For pregnancy category C, if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
2- For pregnancy Category C, if animal reproduction studies have not been conducted with {name of drug}; and It is also not known whether {name of drug} can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

The labeling must state:

1. Pregnancy Category C. {Name of drug} has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in {name(s) of species} when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. {Name of drug} should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. Pregnancy Category C. Animal reproduction studies have not been conducted with {name of drug}. It is also not known whether {name of drug} can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. {Name of drug} should be given to a pregnant woman only if clearly needed.

3. معامل الحمل فئة C

معامل الحمل فئة C له تعريفان:

1- يُعرف معامل الحمل فئة C بأنه إذا أظهرت نتائج الدراسات التي أجريت على أجنحة الحيوانات آثار جينية ولم توجد دراسات سريريّة محكمة وكافية وكانت منافع استخدام الدواء على المرأة الحمل مقبولة إلى حد ما على الرغم من الخطورة المحتملة على الجنين.

2- يُعرف معامل الحمل فئة C إذا لم تجري أي دراسات على أجنحة الحيوانات للدواء {اسم الدواء}. وكذلك لا يعرف إذا كان الدواء {اسم الدواء} يمكن أن يسبب ضرر (أو مخاطر) على الجنين إذا استخدم للمرأة الحامل أو إذا كان له تأثير على مقدرة الحمل.

صيغة كتابة معامل الحمل فئة C في النشرة الدوائية:

1- إذا أظهرت نتائج الدراسات التي أجريت على أجنحة الحيوانات آثارًا جانبية ولم توجد دراسات سريريّة محكمة وكافية وكانت منافع استخدام الدواء على المرأة الحمل مقبولة إلى حد ما على الرغم من الخطورة المحتملة على الجنين.
4. Pregnancy Category D:

For pregnancy category D, if there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

The labeling must state:

“{Name of drug} can cause fetal harm when administered to a pregnant woman. {Describe the human data and any pertinent animal data}. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus”.

4. \(D\) مَعاَلِهُ الْحَمْلُ فَنْفُهُ
5. Pregnancy Category X:

For pregnancy category X, if studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

The labeling must state:

"[Name of drug] may (can) cause fetal harm when administered to a pregnant woman. [Describe the human data and any pertinent animal data]. [Name of drug] is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

صيغة كتابة معامل الحمل فئة D في النشرة الدوائية:

يمكن أن يسبب الدواء (اسم الدواء) ضرراً للجنين عندما ينفي المرأة الحمل. (وصف بيانات الإنسان أو أي بيانات ذات صلة بالحيوان). إذا تم استخدام هذا الدواء أثناء الحمل أو إذا كانت المرأة حاملاً أثناء استعمال هذا الدواء، ينبغي إعلام المريض على الخطر المحتمل على الجنين.

صيغة كتابة معامل الحمل فئة X في النشرة الدوائية:

(اسم الدواء) قد يتسبب في حدوث ضرر للجنين إذا تم استعماله من قبل المرأة الحامل. (وصف للبيانات والمعلومات عن البشر والحيوان) التي ربما تكون ذات صلة بالحيوان. ينفي استعمال (اسم الدواء) في النساء الحوامل أو اللواتي قد يصبحن حوامل. إذا تم استخدام هذا الدواء أثناء الحمل أو إذا كانت المرأة حاملاً أثناء استعمال هذا الدواء، ينبغي إعلامها على الخطر المحتمل على الجنين.
II. The following points must be taken into account when generating the content of product information:

- **Implementing a new section under the title of (Fetal Risk Summary) that includes the following points:**
  - A summary of the risks that occur to the fetus.
  - State any contraindications or precautions for use.
  - Clarify that the use of the drug may worse the risk of developmental abnormalities in addition to other risks (for instance, cancer incidence through the placenta (Transplacental Carcinogenesis) in humans.

- **Use of specific terms for congenital defects to:**
  - Describe the defect in growth (Developmental toxicities), use the term (Developmental anomalies). This includes deformities and disabilities.
  - Describe the defect in shape (Dysmorphogenesis), uses the term (Structural anomalies). This includes deformities and disabilities.
  - Describe the defect in growth (Developmental toxicities), uses the term (Developmental anomalies).
  - Describe the defect in shape (Dysmorphogenesis), use the term (Structural anomalies). This includes deformities and disabilities.
  - Describe the death in growth (Developmental mortality), use the term (Fetal and infant mortality). This includes abortion, stillbirth, and neonatal death.
  - Describe the defect in function (Functional toxicity), use the term (impaired physiologic function). The incidence of deafness and morbidity of the endocrine gland (endocrinopathy), neurodevelopmental effects, and impairment of reproductive function
  - In case of growth retardation, excessive growth and early maturation, use the term (alterations to growth).
- **Point out all known adverse effects that occur to the fetus resulted in the use of medicine during the pregnancy.**

- **Conclusion about risk:**

  Ensure when performing the product information that the use of medication during pregnancy may lead to deformities or development disorders. Stating the mechanism these risks with in terms of doses, duration of exposure during the pregnancy is necessary.

- **Data sources:**

  In developing the fetal risk summary, all available data, including human, animal, and pharmacologic data, that are relevant to assessing the likelihood that a drug will increase the risk of developmental abnormalities or other relevant risks must be considered.

  In deciding whether to prescribe a drug during pregnancy, the clinician needs to consider the human data in combination with the maternal and fetal effects of not treating the maternal condition, other coexisting maternal conditions and/or medications, and whether exposure has already occurred. On the other hand, while the degree to which teratogenesis in animals predicts teratogenesis in humans varies, collective knowledge about the animal species used for reproductive toxicology studies and certain principles of reproductive toxicology provide a basis for more algorithmically characterizing expected risk in the context of animal data. It is important to emphasize that animal data can only predict that a risk exists.

- **Sources of human data:**

  Except for the few products developed to treat conditions unique to pregnancy, prescription drugs are not tested in pregnant women prior to their approval. Therefore, human data concerning a drug’s effect(s) on pregnant women and their offspring almost never come from controlled clinical trials.

- **Risk conclusions based on human data:**

  A) When both human and animal data are available, risk conclusions based on human data must be presented before risk conclusions based on animal data.

  B) A risk conclusion based on human data must be followed by a narrative description of the risk.

  C) When human data are available:
o Those where human data are “sufficient”: sufficient human data are those that are sufficient to reasonably determine the likelihood that the drug increases the risk of fetal developmental abnormalities or specific developmental abnormalities. Sufficient human data may come from such sources as clinical trials, robust pregnancy exposure registries or other large scale, well conducted epidemiologic studies, or case series reporting a rare event.

o And those involving “other human data.”

D) When human data are sufficient, two risk conclusions to be used:

  o When sufficient human data do not show an increased risk, the risk conclusion must state: “Human data do not indicate that {name of drug} increases the risk of (type of developmental abnormality or specific developmental abnormality).” An example of a hypothetical risk conclusion using this statement is: “Human data do not indicate that hypothezine increases the risk of structural malformations.” Another example is: “Human data do not indicate that hypothezine increases the risk of neural tube defects.”

  o When sufficient human data show an increased risk, the risk conclusion must state: “Human data indicate that {name of drug} increases the risk of (type of developmental abnormality or specific abnormality).” An example of a hypothetical risk conclusion using this statement is: “Human data indicate that theoretamine increases the risk of cardiac abnormalities.” Another example is: “Human data indicate that theoretamine increases the risk of hypospadias and clitoral anomalies.”

E) When human data are available but are not sufficient to require the use of one of the two preceding risk conclusions, the likelihood that the drug increases the risk of developmental abnormalities must be characterized as low, moderate, or high. Whether the likelihood of increased risk would be characterized as low, moderate, or high would require a scientific judgment about the quantity and quality of the available data.

F) For cases of other human data, risks should be classified as low, medium, or high.
Risk conclusions based on animal data should be considered and stated in product information, in addition to the following points:

- Product information must be based whenever possible on data derived from human experience. Some of the limitations of animal data concerning the increased risk of developmental abnormalities because of drug exposure have been discussed previously in this document. There is an additional limitation that considered to be particularly important in determining what conclusions can be drawn from animal data regarding human pregnancy outcomes. Toxic drug exposure may manifest as one type of developmental abnormality (e.g., embryolethality) in an animal species, but a different type of developmental abnormality (e.g., structural anomalies) in humans. Thus, it is not possible to draw a conclusion, based on animal data alone. However, it is more concerning when teratogenic effects occur in more than one animal species, especially if these effects were consistent across the different species.

- When the risk conclusion is based solely on animal data, the proposed rule requires that the fetal risk summary component consist only of a risk conclusion and not a description of the effects found in animals. The risk conclusion would be followed by a cross reference to the Data component of the “Pregnancy” subsection, and the effects found in animals would be described in the “Data” component.

- When the data on which the risk conclusion is based are animal data, the fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities using one of the following five risk conclusions:

  a) When animal data contain no findings for any developmental abnormality, the fetal risk summary must state:

      “Based on animal data, {name of drug} is not predicted to increase the risk of developmental abnormalities.”

  b) When animal data contain findings of developmental abnormality but the weight of the evidence indicates that the findings are not relevant to humans (e.g., findings in a single animal species that are caused by unique drug metabolism or a mechanism of action thought not to be relevant to human; findings at high exposures compared with the maximum recommended human exposure), the fetal risk summary must state:
“Based on animal data, the likelihood that {name of drug} increases the risk of developmental abnormalities is predicted to be low.”

c) When animal data contain findings of one or more fetal developmental abnormalities in one or more animal species, and those findings are thought to be relevant to humans, the fetal risk summary must state:

“Based on animal data, the likelihood that {name of drug} increases the risk of developmental abnormalities is predicted to be moderate.”

d) When animal data contain robust findings of developmental abnormalities (e.g., multiple findings in multiple animal species, similar findings across species, findings at low exposures compared with the anticipated human exposure) thought to be relevant to humans, the fetal risk summary must state:

“Based on animal data, the likelihood that {name of drug} increases the risk of developmental abnormalities predicted to be high”.

e) When animal data are insufficient to assess the drug’s potential to increase the risk of developmental abnormalities, the fetal risk summary must state that fact. When there are no animal data to assess the drug’s potential to increase the risk of developmental abnormalities, the fetal risk summary must state that fact.

- **Narrative description of the risks:**
  
  o When human data are available, in addition to the risk conclusion(s), the fetal risk summary must be followed by a brief description of the risks of developmental abnormalities as well as on other relevant risks associated with the drug.
  
  o When appropriate, the description must include the risk above the background risk attributed to drug exposure. For example, the product information might state: “Exposure to Drug X during the first trimester increases the risk of neural tube defects 20-fold, from 10 to 25 defects in 10,000 pregnancies to 200 to 500 defects in 10,000 pregnancies.”
  
  o When appropriate, the description must include confidence limits and power calculations to establish the statistical power of the study to identify or rule out a specified level of risk. For example, the product information might state: “Compared to a 1.62%
prevalence of major malformations in women with the same disease not exposed to the drug, the relative risk of having an affected offspring for Drug X-exposed women is 7.3 (95% CI: 4.4 to 12.2; p<0.001)."

- If there is an information on an increased risk to the fetus from an exposure to a drug in the "Contraindications" or "Warnings and Precautions" sections of the product information the fetal risk summary must refer to the relevant section.
- In case a drug is contraindicated for use in pregnancy in a particular patient population, the product information should describe specifically the population to which the contraindication applies.
- In case a drug poses an increased risk to the fetus only during a particular time period, the time period should be stated in the contraindication section (e.g., first trimester; after 30 weeks).
- The contraindication for use in pregnancy should be based on a determination that the drug should not be used in pregnancy because the risk of use during pregnancy clearly outweighs any possible therapeutic benefit.

### Clinical Considerations:

- Counseling women who were inadvertently exposed to the drug during pregnancy.
- Describing the risks to the pregnant woman or the fetus when making prescribing decisions for pregnant women.
- Describing (in details) the changes that occur in pharmacokinetics of the drug as well as dosing adjustments during pregnancy.
- If use of the drug is associated with maternal adverse reactions that are unique to pregnancy or if known adverse reactions occur with increased frequency or severity in pregnant women, such adverse reactions should be described. This description should include, if known, the effect of dose, timing, and duration of exposure on the risk to the pregnant woman of experiencing the adverse reaction(s). If information is available on interventions that might be needed, language to that effect would also be required.
- If it is known or anticipated that treatment of the pregnant woman will cause a complication in the fetus or the neonate, the labeling would be required to describe the
complication, the severity and reversibility of the complication, and general types of interventions, if any, that may be needed.

- Caution when prescribing drugs during labor and delivery.

**Data:**

- Presenting a brief overview of the data that are the basis for the fetal risk summary and the clinical considerations portion of the product information.
- Describing the studies, including study type(s) (e.g., controlled clinical or nonclinical studies, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies), animal species used, exposure information (e.g., dose, duration, timing), if known, and the nature of any identified fetal developmental abnormalities or other adverse effect(s).
- Describing positive and negative experiences of human data during pregnancy, including developmental abnormalities.
- Describing the relationship of the exposure and mechanism of action in the animal species to the anticipated exposure and mechanism of action in humans.
Developmental toxicities (Developmental abnormalities)

Structural abnormalities (Dysmorphogenesis)

Fetal and infant mortality (Developmental mortality)

Impaired physiologic function (Developmental toxicity)

Alterations to growth (Early maturation)

Sources of human data

Conclusions About Risk:

1. It should be noted that the events related to the use of the drug during pregnancy may lead to developmental or growth disorders or other risks and that these risks are the result of variations in dosage and duration of exposure during pregnancy.

2. It should be noted that the data sources referred to in the human data include:

   a. The available data, including those specific to humans and animals.
   b. Data sources that have direct relevance to the testing of drugs during pregnancy. For example, similar data are found in the literature and in the literature reviewed in this document. Such data are obtained through various methods of testing and are used to determine the risks associated with the use of the drug during pregnancy. However, it should be noted that the information provided is not exhaustive and that further research is needed to fully understand the risks associated with the use of the drug during pregnancy.

3. It should be noted that the data sources referred to in the human data include:

   a. The available data, including those specific to humans and animals.
   b. Data sources that have direct relevance to the testing of drugs during pregnancy. For example, similar data are found in the literature and in the literature reviewed in this document. Such data are obtained through various methods of testing and are used to determine the risks associated with the use of the drug during pregnancy. However, it should be noted that the information provided is not exhaustive and that further research is needed to fully understand the risks associated with the use of the drug during pregnancy.

4. It should be noted that the data sources referred to in the human data include:

   a. The available data, including those specific to humans and animals.
   b. Data sources that have direct relevance to the testing of drugs during pregnancy. For example, similar data are found in the literature and in the literature reviewed in this document. Such data are obtained through various methods of testing and are used to determine the risks associated with the use of the drug during pregnancy. However, it should be noted that the information provided is not exhaustive and that further research is needed to fully understand the risks associated with the use of the drug during pregnancy.
The therapies developed to treat the unique cases of sick individuals and related to the individual differences. If the data obtained from individuals and the related to the effects of the drug on the pregnant woman have not come from weighted and proven studies.

5. It is necessary to consider when writing the publication, an indication to the points related to the risk conclusions based on human data.

A. If the data available to the individual and the animals is not sufficient, the risk summary based on the individual data is provided on the risk summary based on the animal data.

B. It is necessary to follow the risk summary based on the individual data by a description of the risks.

C. If the data available to the individual are different conditions of data:

- The first case if the data are sufficient and confirmed by "increasing the risk of structural abnormalities", which is based on a number of sources such as studies or records of exposure during pregnancy or epidemiological studies that have been conducted on a wide scale or a series of cases that indicate a rare side effect.

- The second case includes "other data available to the individual".

D. In cases of insufficient "individual data", it is used as follows:

- In cases where the individual data do not show an increase in risk, the following sentence is mentioned:

"Human data do not indicate that {name of drug} increases the risk of (type of developmental abnormality or specific developmental abnormality)".

Example of using this sentence is as follows:

"Human data do not indicate that hypothezine increases the risk of structural malformations"

The other example is:

"Human data do not indicate that hypothezine increases the risk of neural tube defects ".

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"Human data indicate that {name of drug} increases the risk of (type of developmental abnormality or specific abnormality)."

Example: Human data indicate that theoretamine increases the risk of cardiac abnormalities.

Example: Human data indicate that theoretamine increases the risk of hypospadias and clitoral anomalies.

6. [Note: insert specific risk statement]

7. [Note: insert specific risk statement]
جب أن يوضح ملخص المخاطر على الجنين (Fetal Risk Summary) أن استخدام الدواء قد يزيد من خطر تشوهات النمو في حالة كان الملخص مبني على البيانات الخاصة بالحيوان ويذكى بواسطة استخدام إحدى ملخصات المخاطر التالية:

أ. في حال عدم احتواء البيانات الخاصة بالحيوان على أي نتائج عن حدوث اضطرابات في النمو فيجب ذكر العبارة التالية في ملخص المخاطر على الجنين:

"بناء على البيانات الخاصة بالحيوان فإنه لا يتوقع أن يزيد الدواء [اسم الدواء] من خطر اضطرابات النمو.

ب. في حال احتواء البيانات الخاصة بالحيوان على نتائج عن حدوث اضطرابات في النمو لكن الأدلة تشير إلى أن النتائج ليست ذات صلة بالإنسان (على سبيل المثال النتائج في سلالة واحدة من الحيوان كان سببها أيضا دوائي فريد أو آلية عمل يعتقد أن ليس لها صلة بالبشر، نتائج في مستويات عالية مقارنة بالحد الأعلى للتعرض المسموح به في البشر) فيجب ذكر العبارة التالية في ملخص المخاطر على الجنين:

"بناء على البيانات الخاصة بالحيوان فإن احتمالية أن يزيد الدواء [اسم الدواء] من خطر اضطرابات النمو تكون منخفضة.

ج. في حال احتواء البيانات الخاصة بالحيوان على نتائج عن حدوث اضطراب واحد أو أكثر في نمو الجنين في سلالة أو أكثر وكان يعتقد أن هذه النتائج ذات صلة بالبشر فيجب ذكر العبارة التالية في ملخص المخاطر على الجنين:

"بناء على البيانات الخاصة بالحيوان فإن احتمالية أن يزيد الدواء [اسم الدواء] من خطر اضطرابات النمو تكون متوسطة.

د. في حال احتواء البيانات الخاصة بالحيوان على نتائج كثيرة عن حدوث اضطرابات في النمو(على سبيل المثال نتائج متعددة، نتائج مقارنة بين أنواع الحيوان، ونتائج لدى التعرض المنخفض للدواء بالمقارنة مع الإنسان) ومن الممكن أن تكون هذه النتائج ذات صلة بالبشر فيجب ذكر العبارة التالية في ملخص المخاطر على الجنين:

"بناء على البيانات الخاصة بالحيوان فإن احتمالية أن يزيد الدواء [اسم الدواء] من خطر اضطرابات النمو تكون عالية.

ه. في حال أن البيانات الخاصة بالحيوان كانت غير كافية لتقييم احتمالية أن يزيد الدواء من خطر اضطرابات النمو فيجب ذكر هذه المعلومة في ملخص المخاطر على الجنين، وفي حال عدم توفر البيانات الخاصة بالحيوان لتقييم احتمالية أن يزيد الدواء من خطر اضطرابات النمو فيجب ذكر هذه المعلومة في ملخص المخاطر على الجنين.
7. يجب أن يأخذ في الاعتبار عند كتابة النشرة الإشارة إلى النقاط المتعلقة بالوصف السردي للمخاطر (description of the risks)

الأتية:

- في حالة توفر البيانات الخاصة بالإنسان بالإضافة إلى ملخص المخاطر فإنه يجب أن يتبع ملخص المخاطر على

الجنين (Summary Risk Fetal) بوصف مختصر عن مخاطر اضطرابات النمو بالإضافة إلى المخاطر الأخرى التي تترافق مع استخدام الدواء.

ب. يجب أن يحتوي الوصف (في حال أمكن ذلك) على المخاطر السابقة التي ترجع للتعرض إلى الدواء (background risk attributed to drug exposure) قبل سبيل المثال يذكر في النشرة الداخلية أن "العوامل X خلال الثالث الأول من الحمل يزيد من خطر حدوث عيب في الأنبوب العصبي ب 20 ضعف وتحدث 10 إلى 25 حالة عيب من أصل 1000 حالة حمل و 200 إلى 500 من أصل 10000 حالة حمل".

ج. يجب أن يتضمن الوصف (في حال أمكن ذلك) حدود الثقة (confidence limits) وحسابات القوة (power) لإرسال القوة الحسابية للدراسة أو استبعاد مستوى معين من المخاطر ، فلغة سبيل المثال يذكر في النشرة الداخلية أن "بالتقديرات مع نسبة التشوهات الرئيسية في النساء الحوامل اللاتي يعانين من نفس المرض ولم يتعرضوا للدواء والتي تقدر ب 11.72٪ فإن الخطر النسبي من وجود درجة متأثرة للمرأة التي تتعرض للدواء هو 7.63 (95% CI: 4.4 to 12.2; p<0.001)

د. في حالة كانت هناك معلومات عن زيادة خطر تعرض للدواء في جزء "موانع الاستخدام" أو "التحذيرات والاحتياطات" فيجب أن يشير إلى ذلك في جزء ملخص المخاطر على الجنين.

ه. في حالة منع استخدام الدواء لفئة معينة من الناس يجب أن يذكر ذلك في النشرة الداخلية للدواء.

و - - في حالة كان الدواء يشكل خطر على الجنين خلال فترة زمنية معينة يجب أن يذكر ذلك في جزء "موانع الاستخدام" (على سبيل المثال الثالث الأول ، بعد 30 أسبوع).

ز - يجب أن يكون دواء مبني على تحديد أن الدواء لا يستخدم خلال الحمل بسبب أن المخاطر الناتجة عن استخدامه تفوق أي منفعة مرجوة.

(Clinical Considerations)

الأتية:

- تقديم المشورة للنساء الحوامل اللاتي تعرضن للدواء بشكل غير مقصود خلال فترة الحمل.

ب. إيضاح المخاطر على المرأة الحامل أو الجنين عند اتخاذ القرارات بشأن وصف الأدوية للنساء الحوامل.

ج. ذكر التغييرات التي تحدث في حركية الدواء بالتفصيل أثناء الحمل واحتمالات تتعديل الجرعة.
د. ذكر الأعراض الجانبية التي تتغير حدتها أثناء الحمل.

ه. إذا كان معروفاً أن معالجة المرأة الحامل سوف تسبب في حدوث مضاعفات للجنين فانه يجب أن يذكر نوع المضاعفات وحدتها وما إذا كانت قابلة للعلاج وكذلك أنواع التدخلات (interventions) العلاجية العامة ومدى الحاجة لها.

و. أخذ الحيطية عند وصف الأدوية أثناء المخاض والولادة.

9. يجب أن يؤخذ في الاعتبار عند كتابة النشرة إيضاح البيانات (Data) الآتية:

أ. تقديم ملخص عن البيانات التي تعتبر المصدر الأساسي لمثل المخاطر على الجنين (Fetal Risk Summary) و الاعتبارات السريرية (Clinical Considerations).

ب. يجب أن يذكر في النشرة نوع أو أنواع الدراسات (مثل الدراسات السريرية المحكمة أو الدراسات الغير سريرية أو الدراسات الويبائية أو السجلات المكتملة)، سلالة الحيوانات المستخدمة، معلومات التعرض للدواء (الجرعة والمدة)، وطبيعية أي اضطراب معروف أو الآثار الجانبية الأخرى.

ج. يجب ذكر المعلومات الخاصة بالإنسان ضمن جزء البيانات (Data) والتي تشمل نتائج الخبرات الإيجابية والسلبية خلال الحمل ومن ضمنها اضطرابات النمو.

د. يجب وصف أشكال التعرض للدواء والآلة عمله في سلالات الحيوانات ومقارنتها مع ما يتوقع حدوثه في الإنسان.
### III. SFDA pregnancy category in corresponding to EMA statements

The following table is a guide to the applicant in case of the product’s labeling based on EMA Regulation.

*Note:* The applicant should generate the content of product information based on the SFDA pregnancy category.

<table>
<thead>
<tr>
<th>SFDA proposed pregnancy category</th>
<th>SFDA proposed statement</th>
<th>EMA statement</th>
</tr>
</thead>
</table>
| **Pregnancy Category A:**
For pregnancy category A, if adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of a risk in later trimesters.

Pregnancy Category A. Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed.

If animal reproduction studies are also available and they fail to demonstrate a risk to the fetus, the labeling must also state:

Reproduction studies have been performed in (kinds of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug).

<No effects during pregnancy are anticipated, since systemic exposure to {Active substance} is negligible>.

{Invented name} can be used during pregnancy. (E.g. medicinal products for which negligible systemic exposure/negligible pharmacodynamic systemic activity has been demonstrated in clinical situation)

| **Pregnancy Category B:**
For pregnancy category B, if animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled

If animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled [1] <A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/
<table>
<thead>
<tr>
<th>to the fetus and there are no adequate and well-controlled studies in pregnant women.</th>
<th>studies in pregnant women, the labeling must state:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.</td>
<td><strong>Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.</strong></td>
</tr>
<tr>
<td>If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state:</td>
<td><strong>If animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters), the labeling must state:</strong></td>
</tr>
<tr>
<td>Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, neonatal toxicity&gt;.</td>
<td><strong>Pregnancy Category B. Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, neonatal toxicity&gt;.</strong></td>
</tr>
<tr>
<td>Animal studies do not indicate reproductive toxicity. The use of {invented name} may be considered &lt;during pregnancy &gt; &lt;during {trimester} of pregnancy&gt;, if necessary. [2] A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity&gt;.</td>
<td><strong>Animal studies do not indicate reproductive toxicity. The use of {invented name} may be considered &lt;during pregnancy &gt; &lt;during {trimester} of pregnancy&gt;, if necessary. [2] A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity&gt;</strong>.</td>
</tr>
<tr>
<td>{Invented name} can be used &lt;during pregnancy &gt; &lt;during {trimester} of pregnancy&gt; if clinically needed</td>
<td><strong>{Invented name} can be used &lt;during pregnancy &gt; &lt;during {trimester} of pregnancy&gt; if clinically needed</strong></td>
</tr>
</tbody>
</table>
(name of drug) should be used during pregnancy only if clearly needed.

**Pregnancy Category C**

There are two conditions for pregnancy category C:

1. For pregnancy category C, if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

2. For pregnancy Category C, if animal reproduction studies have not been conducted with (name of drug); and It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in 16 (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Category C. Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed.

[1] <There are no or limited amount of data from the use of {Active substance} in pregnant women> A <Studies in animals have shown reproductive toxicity (see section 5.3).> [or] B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>

{Invented name} is not recommended < during pregnancy > <during {trimester} of pregnancy > and in women of childbearing potential not using contraception >

[2] <There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of {Active substance} in pregnant women>

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable < to avoid the use of {invented name} <during pregnancy > <during {trimester} of pregnancy >.

[3] <A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or fet/o/...>
For pregnancy category D, if there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks

| Neonatal Toxicity | A: Animal studies have shown reproductive toxicity (see section 5.3). [or]  
|---|---
| B: Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).  
| As a precautionary measure, it is preferable to avoid the use of {invented name} during pregnancy.  
| (Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.  
| [1] Based on human experience (specify) {Active substance} is suggested / suspected to cause congenital malformations (specify) when administered during pregnancy.  
| A: Studies in animals have shown reproductive toxicity (see section 5.3).  
| [or]  
| B: Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).  
| {Invented name} should not be used during pregnancy unless the clinical condition of the woman requires treatment with {active substance}.  
| Women of childbearing potential have to use effective contraception during {number} weeks after} treatment.  
| [2] Based on human experience (specify) {Active substance} is suggested / suspected to cause...
congenital malformations (specify) when administered during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

{Invented name} should not be used during pregnancy unless the clinical condition of the woman requires treatment with {active substance}.

<Women of childbearing potential have to use effective contraception during <and up to {number} weeks after> treatment, >>

Pregnancy Category X

If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit.

(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

< Based on human experience (specify) <{Active substance} causes congenital malformations (specify) when administered during pregnancy.

[or] harmful pharmacological effects during pregnancy and/or on the foetus/new-born child.>

{Invented name} is contraindicated during pregnancy during {trimester} of pregnancy [this case is a strict contraindication] (see section 4.3).

<Women of childbearing potential have to use effective contraception during and up to {number} weeks after> treatment.>>
Appendix 4: Lactation statements

1. {Active substance} is not excreted in breast milk. {Invented name} can be used during lactation.

2. {Active substance} is excreted in breast milk. However, at therapeutic doses of {Invented name} no effects on the suckling child are anticipated. {Invented name} can be used during breast-feeding.

3. {Active substance} is excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of {Invented name} are administered to breast-feeding women.
   
   • Alternative recommendations (combinations of recommendations may be used):
     
     - {Invented name} should not be used during breast-feeding.
     - {Invented name} is contraindicated during breast-feeding (*must also be contraindicated in 4.3*).
     - Lactation should be discontinued during treatment with {Invented name}.
     - A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from {Invented name} therapy.

   • Additional recommendation (if applicable):
     
     - Due to the long retention time of {substance} in the body, breast-feeding must not be resumed until x (days, months) after {Invented name} therapy is completed.

4. It is unknown whether {Active substance} is excreted in human breast milk. The excretion of {Active substance} in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.
5. It is unknown whether {active substance} is excreted in human breast milk. Animal studies have shown excretion of (active substance) in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.

6. It is unknown whether {Active substance} is excreted in human breast milk. Animal studies have not shown excretion of {Active substance} in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.

7. There is insufficient/limited information on the excretion of {Active substance} in human or animal breast milk. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with {Invented name} should be made taking into account the benefit of breast-feeding to the child and the benefit of {Invented name} therapy to the woman.

8. There is insufficient/limited information on the excretion of (active substance) in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on (active substance) point to excretion in breast milk and a risk to the suckling child cannot be excluded. {Invented name} should not be used during breast-feeding.

9. No effects on the suckling child are anticipated since the systemic exposure of the breastfeeding woman to {Active substance} is negligible. {Invented name} can be used during breastfeeding.
   - *E.g. ear and eye drops and other topical drugs for which negligible systemic exposure has been demonstrated.*

10. No effects on the suckling child are anticipated. {Invented name} can be used during breastfeeding.
    - *E.g. most vitamin and mineral formulations.*
Appendix 5: Additional information that are required to be translated into Arabic language

المعلومات الواجب ترجمتها على الملصق الخارجي للمستحضر الصيدلاني باللغة العربية (بالإضافة للمعلومات التي ذكرت سابقاً في الدليل الأساسي)

1. اسم المستحضر وتركيزه
2. الشكل الصيدلاني للمستحضر وحجم العبوة
3. ظروف تخزين المستحضر
4. الشركة الصانعة للمستحضر
5. الشركة المسوقة للمستحضر
6. التسيعة - اسم الوكيل / مالك رخصة التسويق - رقم التسجيل

المعلومات الواجب ترجمتها على شريط المستحضر الصيدلاني باللغة العربية (بالإضافة للمعلومات التي ذكرت سابقاً في الدليل الأساسي)

1. اسم المستحضر وتركيزه

المعلومات الواجب ترجمتها على ملصق العبوات الصغيرة (أقل من 10 مل) باللغة العربية (بالإضافة للمعلومات التي ذكرت سابقاً في الدليل الأساسي)

1. اسم المستحضر وتركيزه
2. ظروف تخزين المستحضر
3. التسيعة - اسم الوكيل / مالك رخصة التسويق - رقم التسجيل
بيانات النشرة الداخلية للمستحضر الصيدلاني (PIL)

معلومات لمستخدم الدواء - النشرة الداخلية للمستحضر الصيدلاني:

{الاسم - التركيز - الشكل الصيدلاني للمستحضر}

{المواد الفعالة}

قم بقراءة هذه النشرة جيداً قبل استعمال أو تناول هذا الدواء

- احتفظ بهذه النشرة، لأنها قد تحتاج إليها لاحقاً.
- في حال كانت لديك أي أسئلة تتعلق بهذا المستحضر قم بإستشارة الطبيب أو الصيدلي.
- إن هذا الدواء قد تم صرفه خصيصاً لك بناءً على وصفة طبية، ولذا يجب عليك عدم إعطائه لأي شخص حتى وإن كان هذا الشخص يعاني من نفس الأعراض التي سبق وأن عانيت منها.
- قم بالإتصال بطبيب المعالج أو الصيدلي في حال زيادة حدة الأعراض الجانبية أو الأصابة بمرض جانبي لم يتم ذكره في هذه النشرة.

تحتوي هذه النشرة على:

1. ما هو اسم المستحضر وما هي دواعي استعماله.
2. قبل القيام بتناول أو استعمال < اسم المستحضر >:
3. طريقة استخدام < اسم المستحضر >.
4. الأعراض الجانبية.
5. ظروف تغذية < اسم المستحضر >.
6. معلومات إضافية.
1. ما هو اسم المستحضر وما هي دواعي استعماله

2. قبل القيام بتناول أو استعمال > اسم المستحضر

   أ - موانع استعمال > اسم المستحضر
   ب - الاحتياطات عند استعمال > اسم المستحضر
   ج - التدخلات الدوائية من أخذ هذا المستحضر مع أي دواء أخرى أو أعشاب أو مكملات غذائية
   د - تناول > اسم المستحضر < مع الطعام والشراب
   ه - الحمل والرضاعة
   و - تأثير > اسم المستحضر < على القيادة وإستخدام الآلات
   ز - معلومات هامة حول بعض مكونات > اسم المستحضر <

3. طريقة استخدام > اسم المستحضر <

   أ - الجرعة الزائدة من > اسم المستحضر <
   ب - نسبين تناول جرعة > اسم المستحضر <
   ج - التوقف عن تناول > اسم المستحضر <

4. الأعراض الجانبية

5. ظروف تخزين > اسم المستحضر <

6. معلومات إضافية

   أ - ما هي محتويات > اسم المستحضر <
   ب - ما هو الشكل الصيدلاني > اسم المستحضر < ووصفه وحجم عبوته
ج - اسم وعنوان مالك رخصة التسويق والمصنع
د - تم الموافقة على هذه النشرة بتاريخ { شهر / سنة } ، { رقم النسخة}

6. الإبلاغ عن الأعراض الجانبية:

المملكة العربية السعودية:

<table>
<thead>
<tr>
<th>المركز الوطني للتبييض والسلامة الدوائية</th>
</tr>
</thead>
<tbody>
<tr>
<td>فاكس: 62-205-11-66+</td>
</tr>
<tr>
<td>هاتف: 2282230-6-11-6666  تحويلة: 2340-2353</td>
</tr>
<tr>
<td>الهاتف المجاني: 8002490000</td>
</tr>
<tr>
<td>البريد الإلكتروني: <a href="mailto:npc.drug@sfda.gov.sa">npc.drug@sfda.gov.sa</a></td>
</tr>
<tr>
<td>الموقع الإلكتروني: <a href="http://www.sfda.gov.sa/npc">www.sfda.gov.sa/npc</a></td>
</tr>
</tbody>
</table>

دول الخليج الأخرى:

الرجاء الاتصال بالمؤسسات والهيئات الوطنية في كل دولة.

8. وضع الإرشادات الصادرة من مجلس وزراء الصحة العرب كما يلي:

<table>
<thead>
<tr>
<th>إن هذا الدواء</th>
</tr>
</thead>
<tbody>
<tr>
<td>الدواء مستحضر يؤثر على صحتك واستهلاكه خلافاً للتعليمات يعرضك للخطر.</td>
</tr>
<tr>
<td>اتبع بدقة وصفة الطبيب وطريقة الاستعمال المنصوص عليها وتعليمات الصيدلي الذي صرفها لك.</td>
</tr>
<tr>
<td>إن الطبيب والصيدلي هما الخبراء في الدواء وبنفجه وضرره.</td>
</tr>
<tr>
<td>لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.</td>
</tr>
<tr>
<td>لا تكرر صرف الدواء بدون استشارة الطبيب.</td>
</tr>
<tr>
<td>لا تترك الأدوية في متناول أطفالك الأصدقاء.</td>
</tr>
</tbody>
</table>

مجلس وزراء الصحة العرب
واتحاد الصيادلة العرب
ملاحظة:

يجب أن تكون النشرة الداخلية للمستحضر الصيدلاني:

- مترجمة بطريقة احترافية (من حيث استخدام المصطلحات العلمية).
- مدققة إملائياً ولفظياً.
- مكتوبة بلغة سهلة ومفهومة للمريض.

ولن يتم النظر في أي نشرة داخلية مقدمة للجنة الخليجة المركزية ما لم تستوفي الشروط السابقة.
Appendix 6: Readability of the label and patient information leaflet (PIL)

Introduction

The main purpose of this document is to provide guidance on how to ensure that the information on the labelling and patient information leaflet (PIL) is accessible to and can be understood by those who receive it, so that they can use their medicine safely and appropriately.

This document is written to assist applicants and marketing authorizations holders when drawing up the labeling and PIL and preparing the mock-ups or specimens of the sales presentations^{1}.

The document is intended to apply to all marketing authorization procedures and to all medicinal products.

A. Recommendations for the PIL

General considerations

The PIL is intended for the patient/user. If the PIL is well designed and clearly worded, this maximizes the number of people who can use the information, including older children and adolescents, those with poor literacy skills and those with some degree of sight loss. Companies are encouraged to seek advice from specialists in information design when devising their house style for the PIL to ensure that the design facilitates navigation and access to information.

The following guidance sets out recommendations on various aspects related to the preparation of PILs. It is aimed at helping applicants/marketing authorization holders to fully comply with the legal requirements and is based on experience where it has been shown that using these techniques optimizes the usability of the PIL.

1. Type size and font

Choose a font which is easy to read. Stylized fonts which are difficult to read should not be used.

It is important to choose a font in which similar letters/numbers, such as “i”, “l” and “1” can be

^{1} A mock-up is a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the labelling text is clear. This mock-up is generally referred to as a paper copy and not necessarily in the material of the sales presentation. A specimen is a sample of the actual printed out outer and immediate packaging materials and PIL (i.e. the sales presentation).
easily distinguished from each other.

The type size should be as large as possible to aid readers. A type size of 9 points, as measured in font ‘Times New Roman’, not narrowed, with a space between lines of at least 3 mm, should be considered as a minimum.

Consideration should be given to using different text sizes to enable key information to stand out and to facilitate navigation in the text (e.g., for headings).

The widespread use of capitals should not be used. The brain recognizes words in written documents by the word shape, so choose lower case text for large blocks of text. However, capitals may be useful for emphasis.

Do not use italics and underlining as they make it more difficult for the reader to recognize the word-shape. Italics, however, may be considered when using Latin terms.

2. Design and layout of the information

The use of “justified” text (that is text aligned to both left hand and right hand margins) should in principle not be used.

Line spaces should be kept clear. The space between lines is an important factor influencing the clarity of the text. As a general rule the space between one line and the next should be at least 1.5 times the space between words on a line, where practical.

Contrast between the text and the background is important. Factors like paper weight, color of the paper, size and weight of the type, color of the type and the paper itself should be considered. Too little contrast between the text and the background adversely affects the accessibility of the information. Therefore, background images should in principle not be placed behind the text since they may interfere with the clarity of the information making it harder to read.

A column format for the text can help the reader navigate the information. The margin between the columns should be large enough to adequately separate the text. If space is limited a vertical line to separate the text may be used. Related information should be kept together so the text flows easily from one column to the next. Consideration should be given to using a landscape layout which can be helpful to patients. Where a multi-lingual PIL is proposed there should be a clear demarcation between the different languages used; all the information provided in each language should be assembled.
3. **Headings**

Headings are important and can help patients navigate the text if used well. Therefore, bold type face for the heading or a different color, may help make this information stand out. The spacing above and below the headings should be consistently applied throughout the leaflet. Same level headings should appear consistently (numbering, bulleted, color, indentation, font and size) to aid the reader.

The use of multiple levels of headings should be considered carefully, as more than two levels may make it difficult for readers to find their way around the leaflet. However, where complex information has to be communicated multiple levels of headings may be needed.

Using lines to separate the different sections within the text can also be helpful as a navigational tool.

4. **Print color**

Accessibility is not only determined by print size. Characters may be printed in one or several colors allowing them to be clearly distinguished from the background. A different type size or color is one way of making headings or other important information clearly recognizable.

The relationship between the colors used is as important as the colors themselves. As a general rule dark text should be printed on a light background. But there may be occasions when reverse type (light text on a dark background) could be considered to highlight for instance particular warnings. In such circumstances the quality of the print will need careful consideration and may require the use of a larger type size or bold text. Similar colors should not be used for the text and background as legibility is impaired.

5. **Syntax**

Some people may have poor reading skills, and some may have poor health literacy. Aim to use simple words of few syllables.

Long sentences should not be used. It is better to use a couple of sentences rather than one longer sentence, especially for new information.

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

When setting out the side effects it is particularly important to consider the order in which they are given so the patients/users may maximize the use of the information. In general, setting out the side effects by frequency of occurrence, starting with the highest frequency, is recommended to help communicate the level of risk to individuals. Frequency terms should be explained in a way patients/users can understand – for example “very common” (more than 1 in 10 patients). However, where a serious side effect exists which would require the patient/user to take urgent action this should be afforded greater prominence and appear at the start of the section. Setting side effects by organ/system/class is not recommended since patients/users are in general not familiar with these classifications.

6. Style

When writing, an active style should be used, instead of passive. For example:

- 'take 2 tablets' instead of '2 tablet should be taken',
- 'you must....' is better than 'it is necessary ...'

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

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

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

Medical terms should be translated into language which patients can understand. Consistency should be assured in how translations are explained by giving the lay term with a description first and the detailed medical term immediately after. On a case by case basis the most appropriate term (lay or medical) may then be used thereafter throughout the PIL in order to achieve a readable text. Make sure that the language used alerts the reader to all the information relevant to him/her, and gives sufficient detail on how to recognize possible side effects and understand
any action which may be necessary.

7. Paper

The paper weight chosen should be such that the paper is sufficiently thick to reduce transparency which makes reading difficult, particularly where the text size is small. Glossy paper reflects light making the information difficult to read, so the use of uncoated paper should be considered.

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

8. Use of symbols and pictograms

The images, pictograms and other graphics can be used to aid comprehension of the information, but these exclude any element of a promotional nature. Symbols and pictograms can be useful provided the meaning of the symbol is clear and the size of the graphic makes it easily legible. They should only be used to aid navigation, clarify or highlight certain aspects of the text and should not replace the actual text. Evidence may be required to ensure that their meaning is generally understood and not misleading or confusing. If there is any doubt about the meaning of a particular pictogram it will be considered inappropriate.

B. Recommendations for the labeling

General considerations

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

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

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

In particular the information presented on small packs will need careful consideration so that the text is presented in as large a type size as possible to reduce the likelihood of medication error.

1. Name of the medicine

The full name of the medicinal product, with its strength and its pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults, should appear on the outer packaging and on the immediate packaging to aid accurate identification of the medicinal product.

Where the medicinal product contains up to three active ingredients, the international non-proprietary name (INN)/common name(s) of these active ingredient(s) should be stated after the full name on the outer packaging and the immediate packaging, unless the INN/common name(s) is part of the name. The INN should be afforded due prominence for safety reasons.

2. Strength and total content

In some cases the packaging may need to contain information on both the quantity per unit volume and on the total quantity per total volume. The total quantity per total volume can be particularly important for safety reasons for injectable products and other medicines available in solution or suspension.

Different strengths of the same medicinal product should be expressed in the same manner: for example 250 mg, 500 mg, 750 mg, 1000 mg and NOT 1 g. Trailing zeros should not appear (2.5 mg and NOT 2.50 mg). The use of decimal points (or comma) should be avoided where these can be removed (i.e. 250 mg is acceptable whereas 0.25 g is not). For safety reasons it is important that micrograms is spelt out in full and not abbreviated. However, in certain instances where this poses a practical problem which cannot be solved by using a smaller type size then abbreviated forms may be used, if justified and if there are no safety concerns.
3. **Route of administration**

This should be as registered in the summary of product characteristics (SPC) only according to the standard terms. Negative statements should not be used: for example “Not for intravenous use”. In principle only standard abbreviations may be acceptable (i.v., i.m., s.c.).

Other nonstandard routes of administration should be spelled out in full. Some routes of administration will be unfamiliar to patients and may need to be explained within the PIL. This is particularly important when medicinal products are made available for self-medication.

4. **Design and layout**

Applicants and marketing authorization holders should make best use of the space available to ensure that the important information is clearly mentioned on prime spaces on the outer and immediate packaging, presented in a sufficiently large type size. Company logos and pictograms may be presented, where space permits, on the outer packaging and on immediate packaging, provided they do not interfere with the legibility of the mandatory information.

Use of a large type size will be appropriate, although other factors may also be important in making the information legible. Consideration should be given to the line-spacing and use of white space to enhance the legibility of the information provided. For some small packs it may not be possible to present all the critical information in the same field of view. The use of any innovative technique in packaging design to aid in the identification and selection of the medicinal product is encouraged. It is also encouraged where space is at a premium.

Colors should be chosen to ensure a good contrast between the text and the background to assure maximum legibility and accessibility of the information. Highly glossy, metallic or reflective packaging should be avoided, as this affects the legibility of the information. Different colors in the name of the product are discouraged since they may negatively impact on the correct identification of the product name. The use of different colors to distinguish different strengths is strongly recommended.

Similarity in packaging which contributes to medication error can be reduced by the judicious use of color on the pack. The number of colors used on packs will need careful consideration as too many colors could confuse. Where color is used on the outer pack it is recommended that it
is carried onto primary packaging to aid identification of the medicine.

Where a multi-lingual outer and/or immediate packaging is proposed there should be a clear demarcation between different languages where space permits.

5. Blister pack presentations

For blister pack presentations it is important that the particulars remain available to the user up to the point at which the last dose is removed. Often it will not be possible to apply all the information over each blister pocket, consequently where a random display of the information is proposed it should frequently appear across the pack. In all cases it will be acceptable to apply the batch number, manufacturing and expiry dates to the end of the blister strip. If technically possible, applying this information to both ends of each strip should be considered. Where a unit-dose blister presentation is proposed all the information required for blister packs must appear on each unit dose presentation.

In addition, blister foils should be printed to ensure maximum legibility of the information using a sufficiently large font.

Color for the text and the font style, should be chosen carefully as the legibility of the text on the foil is already impaired due to the nature of the material. Where possible, non-reflective material or colored foils should be considered to enhance the readability of the information presented and the correct identification of the medicine.

Small containers

Where the labeling particulars cannot be applied in full to the labeling of small containers, the minimum particulars could be considered. Other factors may need to be taken into account such as the amount of information which has to be included and the font size necessary to ensure the legibility of the information.

The criteria for small container status would normally apply to containers of nominal capacity of 10 ml or less.

Innovative pack design is encouraged where space is at a premium (e.g. the use of wraparound or concertina labels). Paper labels are recommended to increase the legibility of the information applied to, for example, ampoules.
Annex 1:

What's New in The GCC Guidance for Presenting the SPC, PIL and Labeling Information (version 2.0)?

Major changes were provided to the past version 1.1 May 17, 2011, specifically in the following sections:

II. Labeling:

1. Particulars to appear on the <outer packaging> <and> <the immediate packaging>
2. Minimum particulars to appear on blisters or strips
3. Minimum particulars to appear on small immediate packaging units

III. Patient Information Leaflet (PIL):

6. Further information:

IV. Summary of Product Characteristics (SPC):

4. Clinical particulars:

13. This summary of product characteristics is approved by the Saudi Food and Drug Authority:

Appendix 3: Pregnancy statements:
References


