PATIENT INFORMATION LEAFLET (PIL) GUIDELINES

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Drug Regulatory Authority of Pakistan
Islamabad-Pakistan

1. HISTORY

This is the first edition of this document.

2. APPLICATION-Guideline for Industry

This document is applicable to the firms who intend to apply for registration / market authorization of pharmaceutical and biological drug products for human use.

3. PURPOSE

The guideline is intended to provide supportive information for the preparation of a Patient Information Leaflet (PIL) for registration/market authorization of pharmaceutical and biological products of all types including New drug products, Generic drug products, and Biosimilars. This guideline provides advice on the principles of presenting information in the PIL.

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4. INTRODUCTION

The Patient Information Leaflet (PIL) is the basis of information for patients for use of drug products ensuring their safety, efficacy and quality. It describes the set of information for patients that ensures the safe and effective use of medicine under most circumstances. The PIL is a document that will be updated as new data emerges related to the safety, efficacy and quality or use of drug product. The registration / market authorization holder shall supply any new information without delay which may require the variation of the marketing authorization / registration including the revision of PIL.

5. LEGAL REQUIREMENTS

i. Rule 26 of the Drugs (Licensing, Registering & Advertising) Rules, 1976, as amended vide S.R.O 713(I)/2018 dated 8th June 2018, under 26(1) section 1.5.14 requires that in order to obtain registration/marketing authorization of drug product, a Patient Information Leaflet (PIL) is required to be included in the application dossier. The PIL is part of drug registration / marketing authorization approval, and its contents can only be changed with the approval of Competent Authority.

ii. Section 7 (c) (ix) of DRAP Act 2012, mandated the systematic implementation of internationally recognized standards of World Health Organization, International Conference on Harmonization (ICH), and Food and Drug Administration guidelines etc.

iii. These guidelines conform to DRAP Act 2012, Drugs Act 1976 and rules framed there under and some parts such as classification, definitions, and description etc., have been adopted from WHO guidelines on registration / market authorization procedures.

6. ACRONYMS & DEFINITIONS

ADR	Adverse Drug Reaction
API	Active Pharmaceutical Ingredient
DRAP	Drug Regulatory Authority of Pakistan
MAH	Marketing Authorization Holder
PiL	Patient Information Leaflet
SmPC	Summary of Product Characteristics

Active Pharmaceutical Ingredient (API)	A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).
Container closure system	A primary container closure system is a packaging component (for example, a vial) that is in, or may come into, direct contact with the final product dosage form, or components that contribute to the container/closure integrity of the primary packaging material for a sterile product. A secondary container closure system is a packaging component (for example, a carton) that is not, and will not be, in direct contact with the dosage form.
Excipient	Material other than the Active Pharmaceutical Ingredient(s) / Drug Substance(s) in the dosage form essentially required in manufacturing of Finished Drug Product.
Finished Drug Product	A product that has undergone all stages of production, including packaging in its final container, labeling, quality control and quality assurance.
Marketing Authorization Holder / Registration Holder	Legal entity that has received marketing authorization/ registration or licensure to manufacture and/or distribute a medicine. It also refers to a legal entity allowed to apply for a change to the marketing authorization or registration. Also referred to as the "manufacturer" or "applicant" in this document if both are same.

7. GENERAL CONSIDERATIONS

Applicants are advised to submit a separate PIL for each strength and dosage form of finished drug product in prescribed format provided as Annexure-I in this document, under Module 1.5.14 as Patient Information Leaflet (PIL).

The applicant shall maintain the integrity of each section of the document by only including information in each section which is relevant to the section heading. However, some issues may need to be addressed in more than one section of the PIL and in such situations the individual statements may cross-refer to other sections when these contain relevant additional information.

The contents of the PIL must be in accordance with the SmPC of the drug product, but the text shall be phrased so that it is readily intelligible for the patient and address the patient or the caregiver. Where a specialized term is used, a lay terminology explanation should be given or it should be in consumer intelligible language.

8. REQUIREMENTS

The following information is required to be submitted under Module 1.5.14 as Patient Information Leaflet (PIL):

1. WHAT {PROPRIETARY / BRAND} IS AND WHAT IT IS USED FOR

The pharmacotherapeutic group or type of activity of the drug product should be stated here using language intelligible to the patient, followed by a brief description of the indications for use of the medicine, as accepted by DRAP.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE {PROPRIETARY / BRAND}

If you are hypersensitive (allergic) to {insert name of the active substance} or any of the other ingredients of {Proprietary / Brand} (listed in section 6). [Include reference to residues, excipients, etc. if applicable].

2.1 Do not use {Proprietary / Brand}

Information on absolute contraindications, in accordance with the SmPC, should be provided here in patient-intelligible language. This should include chronic accompanying diseases (e.g. kidney insufficiency, liver insufficiency, diabetes and other metabolic diseases), contraindications due to interactions with other medicines, contraindications due to excipients and specified conditions for certain categories of users, e.g. children or the elderly.]

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

2.2 Warnings and Precautions

Tell your doctor or health care provider before being given the injection:

Take special care/ Special care should be taken with {Proprietary / Brand}:

- If you …….
- When …….

[Also describe cases (if any) in which the consumer should only use the medicine after consultation with a medical practitioner. Include (as appropriate and if not mentioned in the previous section) reference to chronic accompanying diseases (renal insufficiency, liver insufficiency, diabetes and other metabolic diseases).]

[Where applicable, provide information on necessary examinations, which may be carried out by the medical practitioner prior to, or during, the therapy, for example tests carried out in order to exclude contraindications. Provide information (if there is any) about important symptoms which may be masked by the medicine or if the medicine influences laboratory values. If relevant, reference should be made here to possibilities for intolerance to various materials (e.g. disposable plastic syringes), which must be used as part of the medicine.]

[Refer to the need for the avoidance of external influences, such as sunlight after the use of phototoxic medicines. Other warnings concerning for example other diseases and the influence of the medicine on behavior should be described. Statements should also include for example, reference to discolorations of underwear as a result of changes in the color of urine and stool.]

[in case of anesthetic medicines or medicines used for conscious sedation, include a statement explaining that interference with daily activities may continue for up to 24 hours and no legal / contractual decisions should be entered into for 24 hours after receiving anesthetic / conscious sedation.]

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

[Include whether the medicine may affect the performance of child and adult learning in schools and other institutions of education, learning and training.]

[When the medicine is indicated in children, the warnings and precautions which are specific to this population (and identified as such in section 4.4 of the SmPC) should be included under this sub-heading. Where relevant, parents / caregivers should also be alerted in this section of potential children / teenager specific warnings included under "driving and using machines".]

[If there is no indication in some or all subsets of the pediatric population, information should reflect the pediatric subsection of section 4.2 of the SmPC, e.g. "Do not give {Proprietary / Brand} to children between the ages of x and y <years> <months> because <of the risk of [...]> <it does not work> <the potential benefits are not greater than the risks>, <it is unlikely to be safe>".]

2.3 Other medicines and {Proprietary / Brand}

[The following statement must be included.]

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or alternate medicines.)

[Describe the effects of other medicines on the medicine in question and vice versa. Reference should be made to the intensification / weakening and the prolonging / shortening of effects. This information should be in line with the Interactions as in the SmPC.]

2.4 {Proprietary / Brand} with food and drink

[Interactions not related to medicines should be mentioned here if reference is made in section 4.5 of the SmPC. For example, patients should not consume milk in combination with tetracyclines and no alcohol should be consumed during treatment

with benzodiazepines and other central nervous system depressants. This section should not be used to tell patients whether or not their medicine should be taken before, during or after meals as this should only be addressed in section 3 (below), but a cross-reference to section 3 can be included.]

2.5 Pregnancy, breast-feeding and fertility

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

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.

2.6 Driving and using machines

[Include whether the medicine may affect mental and / or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and / or sound coordination and vision e.g. driving, riding, flying, sailing, operating machines / equipment.]

It is not always possible to predict to what extent {Proprietary / Brand} may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which {Proprietary / Brand} affects them.

3. HOW TO USE {PROPRIETARY / BRAND}

Do not share medicines prescribed for you with any other person.

[The following statements should be included, where applicable.]

[For medicines available on prescription only:]

<Always <take> <use> {Proprietary / Brand} exactly as your doctor <or pharmacist> has told you. Check with your <doctor> <or> <pharmacist> if you are not sure.>

[For medicines available without prescription.]

<Always <take> <use> {Proprietary / Brand} exactly as described in this leaflet or as your <doctor> <,> <or> <pharmacist> <or nurse> <has> <have> told you. Check with your <doctor> <or> <,> <pharmacist> <or nurse> if you are not sure.>

3.1 Dosage

The usual dose is ...

[For medicines available only with a prescription, a statement such as the following should be included on the usual duration of the therapy:]

Your doctor will tell you how long your treatment with {Proprietary / Brand} will last. Do not stop treatment early because ... If you have the impression that the effect of {Proprietary / Brand} is too strong or too weak, tell your doctor or pharmacist.

[For medicines available without prescription:

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

3.2 Administration

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

[Instructions should:

- be used to tell consumers what to do. They should not be used to justify or explain an action
- be described in a practical manner
- tell consumers how to use the medicine properly
- be positive rather than negative, whenever possible. Negative instructions should only be used when the consumer should avoid specific actions
- be given as separate instructions when the consumer is to carry out two separate actions.
- Separate actions should not be compressed into a single sentence
- be numbered and put into the exact order that the consumer should follow
- usually be intelligible without explanations, so as not to overburden consumers with information.]

[Explanations should be used to expand on the reasons for instructions and not to give further information. Instructions may be presented in italics or other type with explanations in plain type, so as to give consumers a guide as to the significance of the information.]

[When applicable, there should be descriptions (with illustrations if useful) of opening techniques for child-resistant containers and other containers to be opened in an unusual manner.] [Some examples of statements that may be included here:]

- Take the tablets with a sufficient quantity of liquid (e.g. one glass of water)
- ... one or two tablets (500 to 1 000 mg of paracetamol) three times a day, this means a daily maximum of six tablets (3 000 mg of paracetamol)
- in the morning, at lunchtime, immediately before meals, with food, after food
- Do not swallow
- Do not chew
- Shake well before use
- Dissolve the effervescent tablet in one glass of water. Then drink the contents of the whole glass
- Take {Proprietary / Brand} once a day, every day, at about the same time each day
- Taking your tablets at the same time each day will have the best effect on your blood pressure. It will also help you remember when to take the tablets
- Allow to reach room temperature before using (e.g. insulins)

[For medicines not self-administered]

[The route of administration should be included} [Include}

You will not be expected to give yourself {Proprietary / Brand}. It will be given to you by a person who is qualified to do so.

[Where applicable, include a cross-reference to Section 6 for any reconstitution instructions]

3.3 If you use more {Proprietary / Brand} than you should

[Description of signs and symptoms of overdosage that the patient is able to recognize and actions to be taken.]

[The following statement must be included.}

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison center.

[For medicines not self-administered]

[The following may be acceptable.]

Since a health care provider will administer {Proprietary / Brand}, he/ she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

3.4 If you forget to use {Proprietary / Brand}

[Provide clear explanations of what should be done following irregular use of the medicine, e.g.:]

Do not take / receive a double dose to make up for forgotten individual doses.

[For medicines not self-administered]

[The following may be acceptable.}

Since a health care provider will administer {Proprietary / Brand}, it is unlikely that the dose will be missed.

3.5 If you stop using {Proprietary / Brand}

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

4. POSSIBLE SIDE EFFECTS

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

{Proprietary / Brand} can have side effects.

[The following statement must be included:]

Not all side effects reported for {Proprietary / Brand} are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking {Proprietary / Brand}, please consult your health care provider for advice.

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

[The information given on side effects should be in accordance with the SmPC. Side effects should be subdivided according to seriousness and frequency, or according to symptom type. Wherever possible, for all side effects the frequency with which they occur must be

mentioned to allow patients to know the risk. Irrespective of their frequency, very serious, side effects of the medicine should be mentioned first or specially emphasized. This applies in particular to side effects where there is an urgent need to take action.]

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

[The risk (frequency) of side effects may be presented using the terms very common (2:1/10); common (2:1/100 to <1/10); uncommon (2:1/1 000 to <1/100); rare (2:1/10000 to <1/1 000); very rare (<1/10 000) if the information is available in the corresponding SmPC.

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

If any of the following happens, stop taking / using {Proprietary / Brand} and tell your doctor immediately or go to the casualty department at your nearest hospital:

- 'swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing',
- 'rash or itching',
- 'fainting'

These are all very serious side effects. If you have them, you may have had a serious reaction to {Proprietary / Brand}. You may need urgent medical attention or hospitalization.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- chest pain,
- angina,
- changes in the way your heart beats, for example, if you notice it beating faster,
- difficulty breathing,
- signs of recurrent infections such as fever or sore throat,
- less urine than is normal for you,
- yellowing of the skin and eyes, dark urine, and tiredness which may be symptoms of liver problems

These are all serious side effects. You may need urgent medical attention.

4.1 Frequent side effects

Tell your doctor if you notice any of the following:

Common/Frequent side effects:

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

4.2 Less frequent side effects

Tell your doctor if you notice any of the following:
Uncommon/Less Frequent side effects:

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

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

4.3 Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects to DRAP through MED Vigilance E-Reporting System of DRAP available online at https://primaryreporting.who-umc.org/PK.

5. HOW TO STORE {PROPRIETARY / BRAND}

[The following statement must be included in this section:]

Store all medicines out of reach of children.

[Where applicable, the following statements may be included.}

[Storage conditions have to concur with those approved in the SmPC]

- Store at or below X°c [Explain ideal storage environment], [For Pakistan all products whose stability studies are conducted as per WHO zone IV-A or IV-B conditions shall be labelled "Store below 30°C"]
- Store at or between 2°c - 8°c (in a refrigerator)
- Store in a freezer
- Do not refrigerate / freeze [as appropriate]
- Store in the original package / container
- Keep the container in the outer carton
- Keep the container tightly closed
- There are no special storage instructions for {Proprietary / Brand}

[An additional short explanation of the storage conditions, in patient-friendly terms, should be included when appropriate, e.g.:]

- Protect from light / moisture
- Do not store in a bathroom
- Do not use after the expiry date stated on the label / carton / bottle

[Where applicable, shelf life after reconstitution, dilution or after first opening the container should be indicated]

[Where appropriate, include a warning against any visible signs of deterioration]

Do not use {Proprietary / Brand} if you notice {provide description of the visible signs of deterioration}

[Information on how to dispose of unused medicine, e.g . .]

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. CONTENTS OF THE PACK AND OTHER INFORMATION

6.1 What {Proprietary / Brand} contains

[Include a full statement of the active substance(s) and excipient(s)J

[The active substance(s) (expressed qualitatively and quantitatively) and the other ingredients (expressed qualitatively) should be identified using their names as given in the SmPC and in the language of the text: e.g.]

- The active substance is ...

- The other ingredients are ... [Include all excipients used in the formulation in accordance with the details provided in SmPC]

[Include any other excipient-related information requirements stipulated by the Drug Act 1976, DRAP Act 2012 and rules framed thereunder.]

[In instances where the patient may need to reconstitute the medicine, include instructions here along with a cross-reference from Section 3]

6.2 What {Proprietary / Brand} looks like and contents of the pack

[A physical description, e.g. shape, colour, texture, imprint, etc., of the dosage form should be included here in accordance with the SmPC.]

[In accordance with information provided in the SmPC, include the pharmaceutical form, the number, volume or mass per package unit, pack size and a description of the packaging material, e.g. bottle, blister pack, etc.]

[In case of a product requiring reconstitution and where the diluent is also provided in the pack, provide description of the diluent in accordance with the SmPC.]

6.3 Marketing Authorisation Holder and Manufacturer

6.3.1 Marketing Authorization Holder

[Details of Registration Holder / Marketing Authorization Holder: As in the SmPC, section 7]

6.3.2 Manufacturer

The name, address and responsibility each manufacturing site involved in production, packaging and testing/batch release of finished product shall be provided.

9. REFERENCES

a. The DRAP Act, 2012.
b. The Drugs Act 1976.
c. The Drugs (Licensing, Registering and Advertising) Rules, 1976.
d. The Drugs (Specifications) Rules 1978.
e. WHO-PQ Recommended Patient Information Leaflet, May 2022.

f. DRAP guidance document for submission of application on Form-5F (CTD) for registration of pharmaceuticals for human use.

g. Guideline for Patient Information Leaflet for Human Medicines (Categories A and D), SAHPRA, September 2022.

ANNEXURE-I

PATIENT INFORMATION LEAFLET

(PROPRIETARY / BRAND) NAME STRENGTH PHARMACEUTICAL FORM

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT {PROPRIETARY / BRAND} IS AND WHAT IT IS USED FOR: -

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE {PROPRIETARY / BRAND}: -

2.1 Do not use {Proprietary / Brand}

2.2 Warnings and Precautions

2.3 Other medicines and {Proprietary / Brand}

2.4 {Proprietary / Brand} with food and drink

2.5 Pregnancy, breast-feeding and fertility

2.6 Driving and using machines

3. HOW TO USE {PROPRIETARY / BRAND}: -

3.1 Dosage

3.2 Administration

3.3 If you use more {Proprietary / Brand} than you should

3.4 If you forget to use {Proprietary / Brand}

3.5 If you stop using {Proprietary / Brand}

4. POSSIBLE SIDE EFFECTS: -

4.1 Frequent side effects

4.2 Less frequent side effects

4.3 Reporting of side effects

5. HOW TO STORE {PROPRIETARY / BRAND}:

6. CONTENTS OF THE PACK AND OTHER INFORMATION: -

6.1 What {Proprietary / Brand} contains

6.2 What {Proprietary / Brand} looks like and contents of the pack

6.3 Marketing Authorisation Holder and Manufacturer: -

6.3.1 Marketing Authorization Holder

6.3.2 Manufacturer

This leaflet was last revised in ……..

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