Guideline for Renewal of Medicines Marketing Authorization

First Edition
December, 2022
Addis Ababa, Ethiopia

ACRONYMS

ACKNOWLEDGEMENTS

Definitions

Contents

1. Introduction 6

2. Guidance for submission of Application 6

3. Requirements for the renewal of Medicine Marketing Authorization 7

3.1. Renewal of the marketing authorization for the product approved under routine procedure 7

3.2. Renewal of the marketing authorization for the product approved under WHO collaborative registration procedure 8

3.3. Renewal of the marketing authorization for the product approved under SRA procedure 8

3.4. Renewal of the marketing authorization for the product approved under conditional approval procedure 8

3.5. Renewal of the marketing authorization for the product approved under Emergency use Authorization procedure 9

4. Process flow and the processing time line 9

5. Annexures 11

ACRONYMS

cGMP	Current Good Manufacturing Practices
EFDA	Ethiopian Food and Drug Administration
MA	Marketing Authorization
NRA	National Medicine regulatory Agencies
SmPC	Summary of Product Characteristics
SRA	Stringent regulatory agency
WHO	World Health Organization

ACKNOWLEDGEMENTS

The Ethiopian Food and Drug Authority (EFDA) would like to acknowledge and express its appreciation to its stakeholders for the financial and technical support delivered in preparation of this Guideline for Renewal of Medicines Marketing Authorization in Ethiopia. The Authority would like to acknowledge also its staff and all who participated in the drafting and its consultative workshops and their respective organizations for their contributions in the development of this document.

Definitions

Applicant

The person or entity who submits a registration application of product to the Authority and responsible for the product information

Authority

The Ethiopian Food and Drug Authority (EFDA)

Authorized local agent (Representative)

Any company or legal person established within a country or jurisdiction who has received a mandate from the manufacturer and/or license holder to act on his behalf for specified tasks with regard to the manufacturer's and/or license holder's obligations under legislation of the medicine and other regulatory guidance's issued by the Authority.

Conditional Approval

Is a time limited provisional marketing authorization procedure of medicine devised to provide access to certain medicines for unmet medical need of the public such as medicines for seriously debilitating disease or life treating disease, those used under emergency situation and orphan medicines, thus providing therapeutic benefit to the patients with potentially very limited alternative choices.

Emergency Use Authorization

An alternative marketing authorization procedure designed to be used for the approval of the medicinal products under emergency situations

1. Introduction

As provided in the proclamation for food and medicine administration Number 1112/2019, article 20 sub article six, every medicine or medical device registered in accordance with this proclamation shall have its registration renewed every five years. According to this provision, a product registration certificate is valid for five years. Therefore, an applicant is required to apply for re-registration of the product that has been on the Ethiopian market for the five years except that when the products were approved under conditional approval or the emergency use authorization procedures.

The marketing authorization issued under conditional approval procedure will remain valid only until the conditions under with the approval was made is fulfilled whereas the emergency use authorization will remain valid as long as the emergency situation declared by the ministry of health is not lifted. However, when such product which get marketing authorization under conditional approval or emergency situation are reported to be an approved product by the other NRA, regional and international bodies, applicant are expected to submit complete dossier through the appropriate application procedures established by EFDA.

2. Guidance for submission of Application

Application for the renewal of the marketing authorization shall be made within 180 days prior to the due date. For the application not submitted within this due date, applicant can still submit application within another 180days provided than applicant has made payment equivalent to the payment set for the new application as per the most current service fee regulation of the Authority. Applications not submitted for renewal within this due date are considered as revoked with the chance for applicant to submit the whole new dossier.

The application for re-registration shall only be made through the electronic information registration system of the EFDA. www.eris.efda.gov.et The application form to be filled will be as per the Annex I of this guideline

The application for re-registration should include Information indicated in Module 1 of the most current medicine registration guideline such as the covering letter, application form (online), declaration that the previous local agent was not changed or an agency agreement if the local agent has been changed, copy of valid GMP certificate or GMP waiver letter issued by the Authority and Declaration letter indicating there is no variation.

If applicant declares variation during the re-registration application, the re-registration processing will be continued whereas the variation will be treated by the variation guideline of the Authority variation.

Therefore, the applicant needs to apply renewal application first and variation application will be followed up on approval of renewal application. In such case applicant is required to make separate payment for the renewal and the variation and the payment shall be made as per the most current service fee regulation of the EFDA.

Applicant shall also provide Tabular summary of any variations notified, accepted, and pending with the Authority since the grant of marketing authorization, if any.

However, if variation is identified by the assessor during the re-registration application the Authority may impose administrative measures or revoke the marketing authorization certificate as per Medicine Marketing Authorization Directive and other relevant law of the Country based on the potential impact of the changes on the product quality, safety and efficacy.

Any technical documents shall not be requested upon re-registration but all necessary administrative documents indicated in module 1 of the dossier as detailed in the most current registration guideline shall be submitted.

3. Requirements for the renewal of Medicine Marketing Authorization

3.1. Renewal of the marketing authorization for the product approved under routine procedure

a) Dated and signed covering letter for submission of the dossier by mentioning the product should be included in the dossier from the manufacturer and/or local agent responsible for registration.
b) Complete application form on eRIS system using https://www.eris.efda.gov.et/login. The application form provided in Annex I may facilitate the filling of the application in the online platform.
c) An agency agreement as detailed in the registration guideline if the Authorized local agent is different from the one applied during the previous registration processing
d) Compliance of the manufacturer with the cGMP requirement:
    - A Copy of valid Good Manufacturing Practice (GMP) and Manufacturing License Certificate of FPP manufacturer issued by the NRA of the exporting country should be provided.
    - A copy of the valid GMP compliance report issued by the EFDA for the re-inspection conducted by EFDA
e) A valid Certificate of pharmaceutical product or marketing authorization certificate should be provided. Certificate of pharmaceutical product as a requirement for registration could be optional provided that valid cGMP Certificate and Market Authorization Certificate from the NRA of exporting country are submitted. When required to be provided, the format and detail of document should be as per the Annex II of this guideline.
f) Product information Product information including package insert, labelling, and summary of product characteristics (SmPC) should be provided in Module 1 of the dossier. All product information label statements are required to be in English and/or Amharic. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification. It is to be noted that a declaration letter indicating that no change has been made to this section of the dossier could be suffice.
g) Evidence for an application fee: Each application should be accompanied by a relevant service fee for registration. Applicants are advised to consult the current

Rate of Service Fees Regulation of the Authority for the amount to be paid for application and contact the Authority for details of mode of payment.

3.2. Renewal of the marketing authorization for the product approved under WHO collaborative registration procedure

a) Documents discussed under 3.1 (a-c) above
b) Compliance of the manufacturer with the cGMP requirement: a copy of the WHO public inspection report should be include in the submission and the copy of this document should be in agreement with the one in the WHO prequalification website.
c) The most recent copy of the Quality information summary
d) The current copy of the WHO public assessment report (WHOPAR) and this should be in line with the one in the WHO prequalification website.
e) Documents discussed under 3.1(g) of this guideline

3.3. Renewal of the marketing authorization for the product approved under SRA procedure

a) Documents discussed under 3.1 (a-c) of this guideline
b) Compliance of the manufacturer with the cGMP requirement: a copy of the valid GMP waiver issued by EFDA.
c) A valid copy of the latest renewal of marketing authorization certificate or equivalent thereof, issued by reference SRA for the product imported from the SRA country listed by EFDA. However, if the manufacturing site is outside the SRA countries listed by EFDA but the manufacturing site have valid GMP certificate issued by one of the NRA listed as SRA, documents discussed under 3.1(e) above should be included in the submission.
d) Written commitment letter to notify the Authority that whenever a pending variation, notice of concern, withdrawal, or recall is initiated to the SRA approvals, the same shall be communicated to the Authority; and,
e) The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling). Note: Applicant should also provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available
f) Documents discussed under 3.1 (g) of this guideline

3.4. Renewal of the marketing authorization for the product approved under conditional approval procedure

The provisional marketing authorization of medicine is limited to a maximum of one year. However, when the conditions required to be fulfilled including additional study data, information and documentations could not be completed within a period decided by the EFDA; applicant should provide adequate scientific justifications to request for extension of submission period one month prior to due date. Once the conditions are fulfilled the product will be issued a marketing authorization under the routine, WHO-CRP or the SRA procedure and the requirements for the then renewal procedure will be as described under 3.1 to 3.3 of this guideline as applicable. The marketing authorization certificate with a validity period of

five years could only be issued after the conditions under which it gets approval are fulfilled within period decided by EFDA.

3.5. Renewal of the marketing authorization for the product approved under Emergency use Authorization procedure

The marketing authorization certificate issued under emergency use authorization will remain valid as long as the emergency situation declared by the ministry of health is not lifted. But, once, the situation is declared as emergency is lifted by the ministry, the applicants should submit the application through either the routine, WHO-CRP or the SRA procedure and the requirements for the then renewal procedure will be as described under 3.1 to 3.3 of this guideline, as applicable.

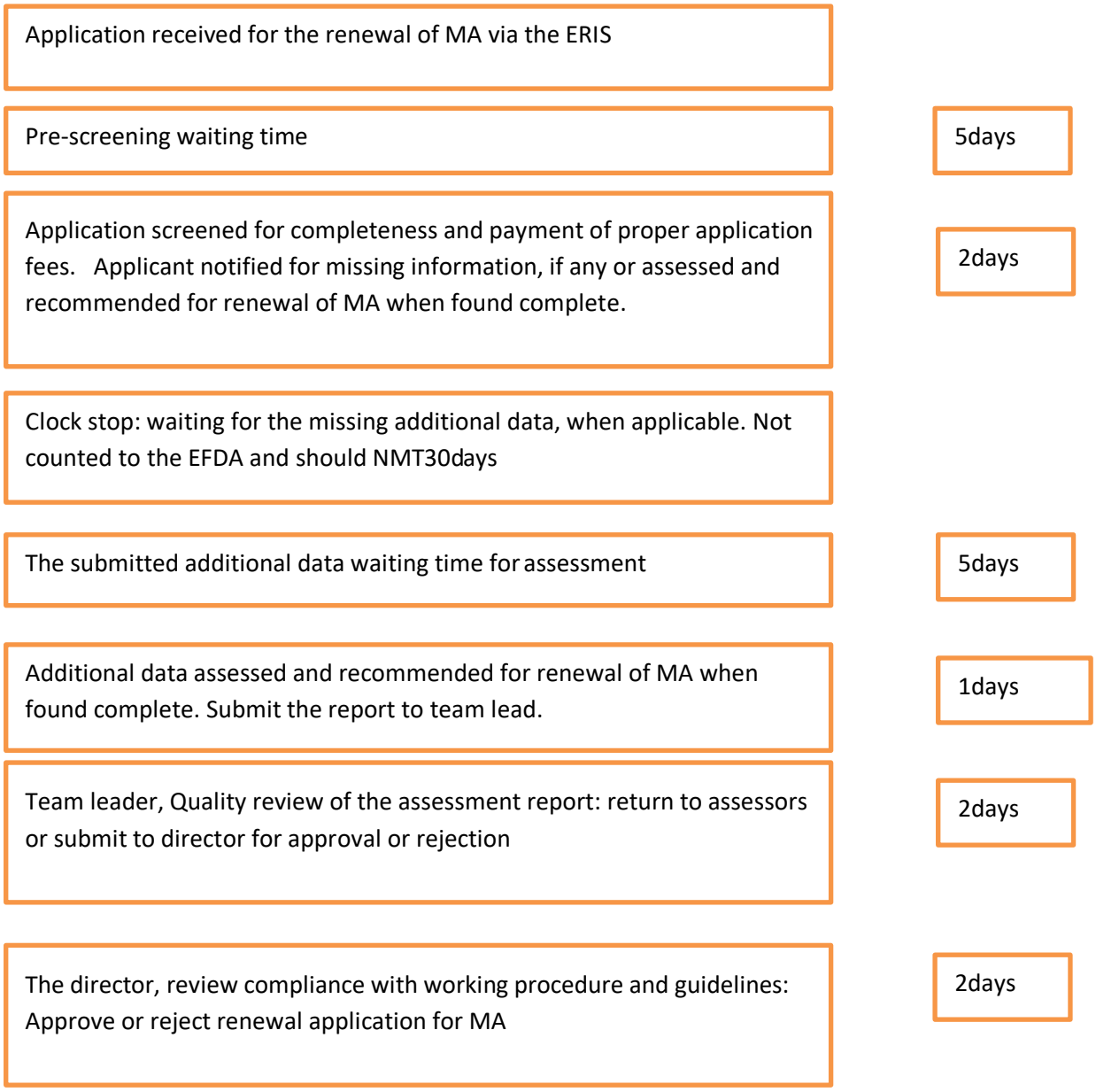
4. Process flow and the processing time line

From the experience developed over the years, it is noted that the actual processing time for the renewal application is a day or two. However, the applications have a waiting time in a queue of application before being assigned and assessed by the assessor. Sometimes the assessors may find missing information from the submitted application or further clarity may be required on certain matters deemed to be necessary based on the observation of the assessor and this will cause a clock stop period and this period are expected to be not more than 30days.

The submitted additional data or information will be also in a queue of additional data or information submission for assessment. It is based on this ground that the processing time for the renewal application from the date of submission of the application is estimated to be 17days. However, the maximum Regulatory processing time for the renewal of application should not be more than 30 working days from the data of submission.

Process flow and the time line for the applications received for the renewal of the marketing authorization will be as indicated below in Figure 1.

Figure 1: Process flow and the time line for the MA renewal applications



5. Annexures

Annex I: Application form

A. Re-registration application for the product approved under (insert √)

Routine procedure	
WHO-collaborative procedure	
SRA procedure	

B. Detail of the product

Proprietary name (trade name)			
Approved generic name (s) (use INN if any)			
Standard claimed (BP, Ph.In, Ph. Eur., USP, IH, etc.)			
Strength(s) per dosage unit			
Dosage form			
Route of administration			
Shelf life (months)			
Storage condition			
Visual description			
Description of container closure			
Packaging and pack size			
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per tablet, per 5ml, etc.). ***Note:*** • ***As many rows and columns as needed could be added/deleted,*** • ***Type of batch should be described***	Composition	Strength	Function
Complete qualitative and quantitative composition (indicate per batch in Kg, L, etc.). ***Note:*** • ***As many rows and columns as needed could be added/deleted,*** • ***Type of batch should be described***	Composition	Strength	Function

Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes			
Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)			

C. Detail of the applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	<< Insert the required information as indicated above >>

D. Detail of Active pharmaceutical(s) ingredient(s) manufacturer

Name of manufacturer	
Street and postal address	
Telephone/Fax number	
E-mail	
Retest period/Shelf life	

E. Detail of local agent (representative) in Ethiopia

Name of local agent	
Sub-city and postal address	
Telephone/Fax number	
E-mail	
Contact person in company Address of company	

F. Details on dossiers submitted with the application

Section of dossier	Page number, Annex, etc of submission
Module 1, as described in this guideline	
declaration that the previous local agent was not changed or an agency agreement if the local agent has been changed	
Tabular summary of any variations notified, accepted, and pending with the Authority since the grant of marketing authorization, if any	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

… is correct and true and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO Guideline, "Good manufacturing practices for pharmaceutical products," is applied in full in all premises involved in the manufacture of this product.
2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.
3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.
4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications before it is released for manufacturing purposes.
5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.
6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.
7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for manufacturing purposes.
8. Each batch of the finished product is either tested or certified against the full specifications in the accompanying documentation and complies fully with the release specifications before it is released for sale.

9. The person releasing the product for sale is an authorized person as defined by the WHO guideline “Good manufacturing practices: Authorized person - the role, functions and training.”
10. The procedures for control of the finished product have been validated for this formulation.
11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.
12. The market authorization holder has a standard operating procedure for handling batch recalls of its products
13. All the documentation referred to in this Certificate is available for review during a GMP inspection.
14. Any clinical trials including bioequivalence study were conducted according to WHO’s “Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.”

Signature_____

Name _____

Position in company (print or type) _____

Date: _____

Annex II: Certificate of Pharmaceutical Products[1]

This certificate conforms to the format recommended by the World Health Organization (General instructions and explanatory notes attached)

No. of Certificate _____
Exporting (certifying country): _____
Importing (requesting country): _____

1. Name and dosage form of the product: _____
1.1. Active ingredient(s)[2] and amount(s) per unit dose[3] : _____ For complete composition including excipients, see attached[4] : _____

1.2. Is this product licensed to be placed on the market for use in the exporting country?[5] **yes/no** (Key in as appropriate)

1.3 Is this product actually on the market in the exporting country? (Key in as appropriate) **yes/no/unknown**

If the answer to 1.2. is **yes**, continue with section 2A and omit section 2B. If the answer to 1.2 is no, omit section 2A and continue with section 2B:[6]

2.A.1. Number of product license[7] and date of issue:

_____
2.A.2. Product license holder (name and address):

_____
2.A.3. Status of product license holder:[8] a/b/c (Key in appropriate category as defined in note 8)
2.A.3.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form:[9]_ _____
2.A.4. Is a summary basis for approval appended?[10] **yes/no** (Key in as appropriate)

2.A.5. Is the attached, officially approved product information complete and consonant with the license?[11] yes/no/not provided (Key in as appropriate) 2.A.6. Applicant for Certificate, if different from license holder (name and address):[12]

_____

2.B.1. Applicant for Certificate (name and address):

_____
2.B.2. Status of applicant: a b/c (Key in appropriate category as defined in footnote 8)

2.B.2.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form:[9] _____

2.B.3. Why is marketing authorization lacking?

not required/not requested/under consideration/refused (Key in as appropriate)

2.B.4. Remarks:[13]

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?

If not or not applicable, proceed to question 4.

yes/no/not applicable[14] (Key in as appropriate)

3.1. Periodicity of routine inspections (years): _____

3.2. Has the manufacture of this type of dosage form been inspected? yes/no

3.3. Do the facilities and operations conform to good manufacturing practices (GMP) as recommended by the World Health Organization (WHO)?[15]

yes/no/not applicable[14] (Key in as appropriate)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product:[16] yes/no (Key in as appropriate)

If no, explain: _____
Address of certifying authority: _____
Telephone: _____
Fax no.:_____
E-mail: _____
Name of authorized person: _____
Signature: _____
Stamp and date: _____

General instructions Please refer to the Guideline for full instructions on how to complete this form and for information on the implementation of the Scheme. This form should always be submitted as a hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations. Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the Certificate in the exporting country. It is for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

[2] Use, whenever possible, the International Nonproprietary Names (INNs) or national nonproprietary names.

[3] The formula (complete composition) of the dosage form should be given on the Certificate or should be appended.

[4] Details of quantitative composition are preferred, but their provision is subject to the agreement of the productlicense holder.

[5] When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is specified in the product license.

[6] Sections 2A and 2B are mutually exclusive.

[7] Indicate, when applicable, if the license is provisional, or the product has not yet been approved.

[8] Specify whether the person responsible for placing the product on the market:

(a) manufactures the dosage form;

(b) packages and/or labels a dosage form manufactured by an independent company; or,

(c) is not involved in any of the above.

[9] This information can only be provided with the consent of the product-license holder or, in the case of nonregistered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product license. If the production site is changed, the license has to be updated or it is no longer valid.

[10] This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

[11] This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the product-license holder. This permission has to be provided to the Authority by the applicant.

[13] Please indicate the reason that the applicant has provided for not requesting registration.

(a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;

(b) the product has been reformulated with a view to improving its stability under tropical conditions;

(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;

(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient; or, (e) any other reason (please specify).

[14] Not applicable means the manufacture is taking place in a country other than that issuing the product Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of drugs referred to in the Certificate are those included in the Thirty-second Report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the

WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[16] This section is to be completed when the product-license holder or applicant conforms to status (b) or (c), as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances, the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

Annex III: Summary of Product Characteristics

(With proposed sentence patterns and illustrative examples)

1. **NAME OF THE FINISHED PHARMACEUTICAL PRODUCT**
   {(Invented) name of product<strength><pharmaceutical form>}
2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   For excipients, see 6.1.
   This include the quantitative composition of special excipients (such as Lactose, Aspartame, Preservative and Antioxidants)
3. **PHARMACEUTICAL FORM**
4. **CLINICAL PARTICULARS**

5.1. Therapeutic indications

<this pharmaceutical product is for diagnostic use only>

5.2. **Posology and method of administration** [See example below.]
Adults
Children and adolescents (4 to 17 years of age)
General administration recommendations
Special dosing considerations in adults

5.3. Contraindications
<Hypersesitivity to the API(s) or to any of the excipients <or {residues}>

5.4. **Special warnings and special precautions for use** [See example below.]
Drug interactions
Acute hemolytic
Hyperglycemia
Patients with coexisting conditions

5.5. **Interaction with other FPPs and other forms of interaction** [See example below.]
Rifabutin)
Ketoconazole)
Itraconazole)
Nevirapine) HMG -CoA reductase inhibitors)
Rifampicin)

4.6. **Pregnancy and lactation** [See example below.]
Use during pregnancy)
Use during lactation)

4.7. Effects on ability to drive and use machines
< {Invented name} has < no or negligible influence> <minor or moderate influence> <major influence> on the ability to drive and use machines.> [describe effects where applicable]
<No studies on the effects on the ability to drive and use machines have been performed><Not relevant]

4.8. **Undesirable effects** [See example below.]
Laboratory test findings)
Post-marketing experience)

4.9. Overdose

<No case of overdose has been reported>

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: {group}

ATC code: {code}

Mechanism of action

Microbiology (when applicable)

Drug resistance (when applicable)

Cross resistance (when applicable)

Pharmacodynamic effects

Adults

Pediatric patients

5.2. Pharmacokinetic properties

Absorption

Distribution

Biotransformation

Elimination Characteristics in patients

5.3. Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.><Preclinical effects were observed only at exposures considered sufficiently in excess of 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.>

Mutagenicity

Carcinogenicity

Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients [See example below.]

Capsule content)

Capsule shell)

Printing ink)

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>

<This pharmaceutical product must not be mixed with other pharmaceutical products except those in 6.6

6.3. Shelf life

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

6.4. Special precautions for storage

<Do not store above <25°C><30°C»

<Store at2°C-8°C (in a refrigerator» <Store in a freezer>

<Do not< refrigerate><or><freeze»

<Store in the original<package><containers><Keep the container tightly closed>

<Keep the container in the outer carton>

<No special precautions for storage>

<in order to protect from <light><moisture>

6.5. **Nature and contents of container**

<Not all pack sizes may be marketed.>

6.6. Instructions for use and handling

7. MARKETING AUTHORISATION HOLDER
8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS
9. DATE OF FIRST AUTHORISATION/RENEWALOF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT

6. References

1. Medicines registration guidelines 2020, 4th Edition
2. Guidelines for conditional approval of Medicines, 2021, 1st Edition
3. Guidelines for Emergency Use Authorization of COVID-19 Vaccine, 2021, 1st Edition