Health Canada Santé Canada

Guidance Document

Product Monograph

Date adopted: 2020-09-10
Effective date: 2020-11-01

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
Ligne Directrice – Monographies de produit

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications@hc-sc.gc.ca

Publication date: November 2020

Cat.: H164-299/2020E-PDF
ISBN: 978-0-660-35885-7
Pub.: 200165

Document change log

Version	Document Name	Change Made	Dates
1	Guidance for Industry: Product Monograph	Initial Issuance of Guidance and Templates	**Adopted Date** 2003/09/22 **Effective Date** 2004/10/01
2	Guidance Document: Product Monograph	Overdosage section • Addition of standard boxed message • Reporting Suspected Side Effects • Administrative updates	**Effective Date** 2010/01/01
3	Guidance Document: Product Monograph	Patient Medication Information (PMI) • Part III, formerly titled 'Consumer Information' was revised to include plain language elements, including new language and formatting	**Adopted Date** 2013/09/12 **Effective Date** 2014/06/01
4	Guidance Document: Product Monograph	Part I: Health Professional Information Part II: Scientific Information Appendices A, B, C, D All 5 associated templates • These sections were revised with plain language enhancements including reorganization of information	**Adopted Date** 2016/06/17 **Revised Date** 2016/12/09 **Effective Date** 2017/06/09
5	Guidance Document: Product Monograph	Formatting and administrative changes throughout guidance document • Removal of appendices; integration of information from appendices into the body of the guidance document • New examples added to improve understanding • New single "master" template to replace previous templates • Section numbering aligned between the guidance and the master template • Boxed NOCc message has been removed from Part II: Scientific Information Instruction added related to Notifiable Change submissions Instruction added related to traceability of vaccines	**Adopted Date** 2020/09/10 **Effective Date** 2020/11/01

Foreword

Guidance documents are meant to provide assistance to industry and healthcare professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable Guidance documents.

Table of contents

1 INTRODUCTION 8
1.1 Purpose 8
1.2 Scope and application 8
1.3 Policy statements 8
1.3.1 What is a product monograph? 8
1.3.2 Medical and scientific implications 8
1.3.3 Regulatory implications 9
1.3.4 Provision of information 9
1.4 Revisions 10
1.5 Distribution 10
1.6 Inquiries 11
1.7 Guiding principles 11
1.8 Using the master template 11
2 PREPARING A PRODUCT MONOGRAPH 12
2.1 General instructions 12
2.2 Style guide 13
TITLE PAGE 14
RECENT MAJOR LABEL CHANGES 16
TABLE OF CONTENTS 18
PART I: HEALTH PROFESSIONAL INFORMATION 18
1 INDICATIONS 18
1.1 Pediatrics 19
1.2 Geriatrics 20
2 CONTRAINDICATIONS 20
3 SERIOUS WARNINGS AND PRECAUTIONS BOX 20
4 DOSAGE AND ADMINISTRATION 21
4.1 Dosing considerations 21
4.2 Recommended dose and dosage adjustment 21
4.3 Reconstitution 22
4.4 Administration 23
4.5 Missed dose 24

4.6 Image acquisition and interpretation 24
4.7 Instructions for preparation and use 24
4.8 Radiation dosimetry 24
5 OVERDOSAGE 25
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 25
6.1 Physical characteristics 26
6.2 External radiation 27
7 WARNINGS AND PRECAUTIONS 27
7.1 Special populations 30
7.1.1 Pregnant women 30
7.1.2 Breast-feeding 31
7.1.3 Pediatrics 32
7.1.4 Geriatrics 32
8 ADVERSE REACTIONS 33
8.1 Adverse reaction overview 35
8.2 Clinical trial adverse reactions 36
8.2.1 Clinical trial adverse reactions – pediatrics 36
8.3 Less common clinical trial adverse reactions 38
8.3.1 Less common clinical trial adverse reactions – pediatrics 38
8.4 Abnormal laboratory findings: hematologic, clinical chemistry and other quantitative data 38
8.5 Post-market adverse reactions 39
9 DRUG INTERACTIONS 39
9.1 Serious drug interactions 39
9.2 Drug interactions overview 39
9.3 Drug-behavioural interactions 40
9.4 Drug-drug interactions 40
9.5 Drug-food interactions 41
9.6 Drug-herb interactions 41
9.7 Drug-laboratory test interactions 41
10 CLINICAL PHARMACOLOGY 41
10.1 Mechanism of action 42
10.2 Pharmacodynamics 42

10.3 Pharmacokinetics 42
11 STORAGE, STABILITY AND DISPOSAL 44
12 SPECIAL HANDLING INSTRUCTIONS 45
PART II: SCIENTIFIC INFORMATION 45
13 PHARMACEUTICAL INFORMATION 45
14 CLINICAL TRIALS 46
14.1 Efficacy and safety studies 46
14.2 Study results 47
14.3 Comparative bioavailability studies 48
14.4 Immunogenicity 48
14.5 Clinical trials - reference biologic drug 49
15 MICROBIOLOGY 49
16 NON-CLINICAL TOXICOLOGY 49
16.1 Comparative non-clinical pharmacology and toxicology 50
16.1.1 Comparative non-clinical pharmacodynamics 51
16.1.2 Comparative toxicology 51
17 SUPPORTING PRODUCT MONOGRAPHS 51
PATIENT MEDICATION INFORMATION 51
Introduction 51
Language 52
Style guide 52
Using the template 54
GLOSSARY 60

1 INTRODUCTION

1.1 Purpose

The purpose of this guidance document is to assist sponsors in developing product monographs with acceptable format and content. Health Canada reviews the product monograph as part of the drug review process, as it forms an integral part of a new drug submission. A product monograph is intended to provide the necessary information for the safe and effective use of a new drug and also to serve as a standard against which all promotion and advertising of the drug can be compared.

This guidance document supersedes the Guidance Document: Product Monograph (2014) and the Guidance Document: Product Monograph (2016) for all drug product submissions identified under section 1.2 Scope and application.

1.2 Scope and application

A draft copy of the proposed or revised product monograph should be included in the master volume when a New Drug Submission (NDS), Supplement to a New Drug Submission (SNDS), Abbreviated New Drug Submission (ANDS) or Supplement to an Abbreviated New Drug Submission (SANDS) is filed for either a prescription or nonprescription drug. Health Canada will advise the sponsor if the submission is judged to be incomplete in complying with the requirements of Section C.08.002 or C.08.003 of the *Food and Drug Regulations*.

1.3 Policy statements

1.3.1 What is a product monograph?

A product monograph is a factual, scientific document on a drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug.

A product monograph should include appropriate information respecting the name of the drug, its therapeutic or pharmacologic classification, its actions and/or clinical pharmacology, and its indications. The product monograph should also include: contraindications, dosage and administration, symptoms and treatment of overdosage, dosage forms, warnings, precautions, adverse reactions, drug interactions, effects on laboratory tests, storage and stability, special handling instructions, pharmaceutical information, information on clinical trials, microbiology, toxicology, and information for the patient. In addition, the product monograph should state both the dates of initial approval and, when applicable, the date of last revision.

1.3.2 Medical and scientific implications

From a medical and scientific standpoint, the prime objective of a product monograph is to provide essential information for healthcare professionals, patients and consumers that may be required for the safe and effective use of a drug.

The information provided should be as meaningful and helpful as possible. However, only those indications that are based on substantial evidence of efficacy and safety and that are the subject of an NDS, or an ANDS, or a Supplement to either submission that has received a Notice of Compliance (NOC) pursuant to Section C.08.004 of the *Food and Drug Regulations*, should be included in the product monograph. The product monograph is not intended to serve as a repository of all information currently available on a drug.

1.3.3 Regulatory implications

The product monograph, as a document, will be included by Health Canada as part of the NOC respecting an NDS or, when appropriate, an SNDS, an ANDS or a Supplement to an ANDS.

The product monograph serves as a standard against which all promotional material, or advertising distributed or endorsed by the sponsor about the drug can be compared. The product monograph serves the following purposes:

- It contains all the representations to be made in respect of the new drug as required by paragraph C.08.002(2)(k) and C.08.003(2)(h) of the *Food and Drug Regulations*.
- It fulfils the requirements for adequate directions for use for new drugs included in a number of sections having to do with labelling in Parts C and G of the Food and Drug Regulations.
- It identifies the information that is to be provided on request when a package insert is not included with a new drug product and a health professional requests information relevant to clinical use.
- It identifies the information that should be provided to the patient respecting the use of that product [that is (i.e., Patient Medication Information].
- It establishes the limitations/parameters for all advertising, representations, and promotional or information material distributed or otherwise endorsed by the sponsor. Subsection C.08.002(2) of the *Food and Drug Regulations* prohibits the advertising of a new drug for any use of the drug or for any claim that has not been the subject of a cleared submission. As this information is represented in the product monograph, no professional or published literature should be quoted, distributed, or otherwise provided by the sponsor if it refers to claims or indications for use that are not supported by the current product monograph.

1.3.4 Provision of information

Information in the product monograph is organized in a manner appropriate for the intended audience.

Prescribing Information

The information described in Part I: Health Professional Information of the product monograph contains prescribing information, and serves the following purposes:

- It identifies the information to be provided if a package insert is included with a new drug product.
- It identifies information to be provided as part of all professional material and that may be used for promotional and advertising purposes.

In addition to Part I, the information described in the Patient Medication Information section may also be provided as part of the package insert for a new drug product.

Patient Medication Information

The information described in the Patient Medication Information section of the product monograph contains information for the patient or consumer. This section identifies the information that is to be provided to the patient or consumer either at the time of dispensing as a separate document, or as a package leaflet.

1.4 Revisions

A product monograph can be revised by filing an acceptable SNDS or SANDS. Revisions should be initiated by the sponsor any time updating of the product monograph is required to incorporate additions or other changes related to safety (particularly with respect to warnings, precautions, adverse reactions, and mode of administration) that may be necessary as a result of newly available information. In some instances, it may be necessary to inform the healthcare professional or the patient about special hazards or to issue special warnings before there is an opportunity to revise the product monograph.

The product monograph should also be revised whenever substantial information is available to support new indications or when other changes or deletions in 1 INDICATIONS are required as a result of additional available information.

Revisions to the product monograph must be in compliance with the Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/safety-efficacy-document.html), the Post-Notice of Compliance (NOC) Changes – Quality Guidance (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html), and the Questions and Answers: Plain Language Labelling Regulations for Prescription Drugs (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/questions-answers-plain-language-labelling-2019/document.html) document.

Pursuant to paragraph C.08.006(f) of the *Food and Drug Regulations*, Health Canada may request that the sponsor revise the product monograph if, on the basis of new information, it is considered to be false, misleading, or incomplete in any respect. Whenever periodic reports on a drug are requested pursuant to paragraph C.08.008(a) of the Food and Drug Regulations, the sponsor should determine whether significant changes should be made in the product monograph as a result of the additional information available.

1.5 Distribution

A copy of the most recently updated product monograph (including the Patient Medication Information) should be provided by the sponsor to healthcare professionals whenever they request prescribing information or other information relevant to the clinical use of the drug. For products that have received an NOC and are marketed, the product monograph must be available in both official languages.

The Health Professional Information portion of the product monograph may also be made available as a package insert. This portion should therefore be provided in connection with the promotion or advertisement of the drug or included in reference manuals distributed or endorsed by the sponsor. In addition the Patient Medication Information may also be provided as part of the package insert for a drug product.

A copy of the most recently updated product monograph (including the Patient Medication Information) should be provided to healthcare professionals prior to, or coincident with, the first direct promotion or marketing of a new drug, and to any healthcare professionals to whom the sponsor sells a new drug before it is generally available.

Additional information may be found in Health Canada's Guidance Document: Labelling of Pharmaceutical Drugs for Human Use (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/labelling-pharmaceutical-drugs-human-use-2014-guidance-document.html).

1.6 Inquiries

The Regulatory Project Management Division of the Therapeutic Products Directorate (TPD) or the Office of Regulatory Affairs of the Biologic and Radiopharmaceutical Drugs Directorate (BRDD) may assist sponsors with questions concerning the filing of a draft product monograph. General inquiries may be directed to hc.rpmd-dgpr.sc@canada.ca or hc.brdd.ora.sc@canada.ca.

1.7 Guiding principles

A product monograph should be prepared with the following guiding principles as a basis for the information:

- Avoid duplication of information. Wherever possible, information should only be presented once in the product monograph.
- Key information should be easy to locate.
- Information should be presented in a consistent format to facilitate ease of retrieval, particularly in an electronic environment. This requires the standardization of terminology and the inclusion of hyperlinks for searching.

1.8 Using the master template

A product monograph should be prepared in the same software format as the other submission documents. An electronic template in Microsoft Word® format is provided on the Health Canada website.

Instructions that may be useful in preparing the product monograph are contained within square brackets […] in the Microsoft Word® template. Information to be added to the product monograph by the sponsor is also indicated within square brackets […]. These brackets are to be removed by the sponsor during preparation.

2 PREPARING A PRODUCT MONOGRAPH

Each product monograph will consist of three distinct parts:

PART I: HEALTH PROFESSIONAL INFORMATION
Contains information required for the safe and appropriate prescribing, dispensing and administering of the drug product.

PART II: SCIENTIFIC INFORMATION
Contains more in-depth scientific/research information such as non-clinical toxicology and data from animal studies and human clinical trials. It complements and extends the information contained in Part I.

PATIENT MEDICATION INFORMATION
Contains information derived from Parts I and II that helps the patient understand what the medication is, how to use it and what the potential side effects are. It is also intended to serve as a guide for healthcare professionals to easily identify the information needed for counselling patients. It is presented in a language and format that is appropriate for a patient audience, including the general public. Patient Medication Information is required for all drugs, regardless of the location of use [for example (e.g.), hospital] or method of administration (e.g., by a third party).

2.1 General instructions

The guidance document presents the sections of the product monograph in the order that they should appear. Sections and their headings should not be omitted, with the exception of 3 SERIOUS WARNINGS AND PRECAUTIONS BOX (i.e., only if there is no Serious Warnings and Precautions Box) and 17 SUPPORTING PRODUCT MONOGRAPHS (i.e., only if there are no supporting product monographs). Sections should not be renumbered or modified as they are expected to be consistent across all product monographs. For example, “4 DOSAGE AND ADMINISTRATION” is always section number 4.

Certain subsections not applicable to a specific drug product may be deleted. For example, "4.8 Radiation Dosimetry" may be deleted if the product is not a radiopharmaceutical. The numbering for remaining subsection headings does not change. The following statement should be included before the Table of Contents:

> *Sections or subsections that are not applicable at the time of authorization are not listed.*

Health Canada recognizes that this guidance document may not address the information requirements for all drugs and individual judgement remains critical in assessing how or whether to present the information. If information is not available for a section, a rationale should be provided by the sponsor. One of the following or similar statements should be included in the applicable section:

> *The clinical trial data on which the original indication was authorized is not available.*
>
> or
>
> *This information is not available for this drug product.*

- "Health professional" is the preferred term that should be used in Part I (Health Professional Information) and Part II (Scientific Information) of the product monograph when referring collectively to professionals. It is also intended to be used in place of singular terms such as: healthcare provider, healthcare practitioner, etcetera (etc.).
- For pharmaceutical prescription products and those administered or obtained through a health professional, the product monograph should be supplied to Health Canada in both official languages (i.e., Canadian English and French). Please refer to the Guidance Document Questions and Answers: Plain Language Labelling Regulations (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/questions-answers-plain-language-labelling-2019/document.html) for more details regarding the timing of the submission of these documents.
- Suggested standard statements are provided for sponsors to use in the preparation of the product monograph. They are identified in the guidance document by the preceding instruction: "the following or similar statement". If a standard statement is applicable, the sponsor is required to use it. If a statement does not fit a particular product, the sponsor may amend it.
- Words or phrases that lack a commonly understood meaning (e.g., imprecise quantitative terms), are not easily defined, are vague, misleading, or promotional in tone should be avoided (e.g., unique, novel, convenient, potent).

2.2 Style guide

- Paper: 21.6 x 27.9 centimetre (8½ x 11") portrait orientation
- Margins: 2.5 centimetre (1") top, bottom and sides
- Line spacing: single
- Font: All sections: Sans Serif type fonts (e.g., Calibri 12 point, Arial 11 point); Patient Medication Information as leaflet: Sans Serif type fonts, text – 10 point, tables - 9 point.
- Justification: left
- Page numbers: on bottom right hand side
- Start each Part on a new page
- Heading format: see template
- When a cross-reference is included, a hyperlink should be built in.
- For Parts I and II, the first use of the brand name should be followed by the proper name (or common name, where there is no proper name) in final dosage form, in parentheses. In describing the drug's actions, pharmacology, and toxicology, the proper name (or common name, where there is no proper name) in final dosage form should be used.
- For Patient Medication Information, brand name should be used to describe the drug, or if there is no brand name, use the proper name of the drug in final dosage form. Where there is no proper name, use the common name in final dosage form.
- Upper case font and bold type face should be used for emphasis sparingly.
- Paragraph numbering should not be used.
- If abbreviations are used in a table, a legend should be included at the bottom of table.

Additional style instructions are provided within the Patient Medication Information.

TITLE PAGE

The title page should bear the following information in the following sequence:

a) the words “Product Monograph, Including Patient Medication Information”,
b) the scheduling symbol (e.g., Pr, N, T/C), as applicable,
c) the brand name of the drug product,
d) the proper or common name of the drug product(s) in final dosage form,
e) the strength(s), dosage form(s) and route(s) of administration (see examples below),
f) where there is no proper or common name for the drug product in final dosage form, list all medicinal ingredients by their proper or common name, along with the dosage form of the final drug product,
g) the pharmaceutical standard of the drug product (e.g., prescribed, pharmacopeial or professed), if applicable,
h) the therapeutic, diagnostic or pharmacological classification and code in accordance with the World Health Organization's Anatomical Therapeutic Chemical (ATC) index[1].
i) the name, place of business and website of the sponsor, and, when appropriate, the name and place of business of the distributor in Canada,
j) date: for a new product monograph provide the “Date of Initial Authorization”. For subsequent revisions to any part of the product monograph, the date of initial authorization is kept and is followed by the “Date of Revision” which is the date of the most recently authorized product monograph; and,
k) the submission control number.

When the title page would normally be omitted (i.e., in package inserts or advertising copy) items a to k should be repeated on page 1 of the product monograph.

For products granted a Notice of Compliance with Conditions (NOC/c) authorization, the following boxed information should be included on the title page (see template).

“[Brand name], indicated for:

- [ ]

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for [Brand name] please refer to Health Canada’s Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html”

[For market authorizations without conditions]

“[Brand name] indicated for:

- [ ]

has been issued market authorization without conditions.”

Presentation: see template

Examples

Quantity should be expressed per dosage unit, per unit volume or per unit weight, using internationally recognised standard terms. The quantity of the active substance should be related to the declaration of product strength.

The strength of a medicinal product should be relevant for its identification and use and should be consistent with the quantity stated in the quantitative composition and in the dosage. The quantitative composition should be expressed in terms of the mass of the active moiety.

Overages or overfills should not be included when stating the quantity of the active substance, because they are not intended for administration and may cause confusion regarding the final deliverable quantity of active substance. However, in cases where the presence of overfill is obvious (e.g., when reconstituting or handling the product), it may be mentioned qualitatively in the relevant section.

- Drug XY 600 mg/300 mg film-coated tablets
  [where each film-coated tablet contains 600 mg of X (as sulfate) and 300 mg Y]
- Drug XYZ 600 mg X, 200 mg Y and 150 mg Z (as 153.2 mg Z sodium)
- Drug IV 2 g iv (as iv sodium)/per vial [or] 2 g/mL after reconstitution
- Drug Nasal Spray 0.1 mL (10 mcg) drug per spray [or] per compression/actuation
- Micrograms should be spelled out in full, or abbreviated as “mcg” only

For salts or hydrates:

- 50 mg A (as citrate) or A citrate equivalent to 50 mg A

For transdermal patches:

- Each patch contains 750 micrograms of estradiol in a patch size of 10 x 10 cm, releasing 25 micrograms of estradiol per 24 hours

For immunoglobulins:

In the case of normal immunoglobulins, the IgG subclass distribution should be stated in terms of percent of total IgG present[2]. The upper limit of the IgA content should also be stated.

For vaccines:

The content of active substance per dose unit (e.g., per 0.5 mL) should be stated. Adjuvants, if present, should be stated qualitatively and quantitatively[2].

For biologics:

The origin of active substance should be defined, including the nature of any cellular systems used for production, including the use of recombinant DNA technology as appropriate (for example, produced in chick-embryo cells)[2].

Immediately following the Title Page, for all products authorized under the Notice of Compliance with Conditions policy, include the following information:

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

List the section headings in the product monograph where any major label changes related to safety and efficacy have been made within the past 24 months, under the following sections only:

- Indications
- Contraindications
- Serious Warnings and Precautions Box
- Dosage and Administration
- Warnings and Precautions

Major label changes include Level I changes filed with an SNDS or SANDS for either a prescription or non-prescription drug. Criteria for determining the levels or types of changes are described in both the Guidance Document: Post Notice of Compliance (NOC) Changes: Safety and Efficacy Document (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/safety-efficacy-document.html) and the Guidance Document: Post Notice of Compliance (NOC) Changes: Quality Document (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document/guidance.html).

The headings of the changed sections (including subheadings where applicable) should be listed in the order in which they appear in the product monograph, on separate lines. The dates should be in the following format: MM/YYYY, and correspond with the authorization date. The section numbers should be included as well. For example:

1 Indications, 1.1 Pediatrics	12/2018

If there were multiple changes under the same heading or subheading within the past 24 months, only list the date of the newest change. For example:

4 Dosage and Administration	12/2018

If there were changes under more than one subheading within the same section during the last 24-month period, list each of these changes separately. For example:

7 Warnings and Precautions, 7.1.1 Pregnant Women	12/2019
7 Warnings and Precautions, 7.1.3 Pediatrics	09/2018

When a new indication is authorized with the filing of an SNDS or SANDS, new information is often added to other sections of the PM, such as Dosage and Administration, Adverse Reactions, and Clinical Trials in addition to the Indications section. In these instances, if any changes are made to the five applicable sections, those must also be reflected. For example:

1 Indications, 1.1 Pediatrics	08/2019
4 Dosage and Administration	08/2019

All major label changes made in the last 24 months should also be indicated within the body of the product monograph where they occur, with a vertical line on the left edge of the page, to alert the reader to the new information. For example:

> 1.1 Pediatrics
>
> Based on the data submitted, the safety and efficacy of Drug X is indicated in pediatric patients ≥ 12 years of age for the treatment of [illness or condition] (see 14 CLINICAL TRIALS) .
>
> The safety and efficacy of Drug X in pediatric patients < 12 years of age have not been established.
>
> 4.2 Recommended Dose and Dose Adjustment
>
> In pediatric patients ≥ 12 years of age, the recommended dose of Drug X is one 100 mg tablet taken orally, once daily with or without food for 4 weeks. No dose adjustments are required.

All Recent Major Label Changes must remain listed for at least 24 months after the date the label change was authorized. Once the 24 month period expires, the sponsor may choose to file a submission to remove the listing, or wait until the next filing to remove it. For subsequent submissions, all major label changes that were authorized within the last 24 months of the filing date should remain listed as Recent Major Label Changes, including the vertical line to the left of the text within the body of the product monograph where these changes occur.

When a Recent Major Label Change has been removed, a sponsor may choose to keep it listed until a subsequent submission is filed. If this is the case, "[Removed]" is placed adjacent to authorization date as follows:

3 Serious Warnings and Precautions Box, Lactic Acidosis	[Removed] 04/2019

Presentation: list (see template)

TABLE OF CONTENTS

Sections and their headings should not be omitted from the Table of Contents, with the exception of 3 SERIOUS WARNINGS AND PRECAUTIONS BOX (i.e., only if there is no Serious Warnings and Precautions Box) and 17 SUPPORTING PRODUCT MONOGRAPHS (i.e., only if there are no supporting product monographs). Section headings should not be renumbered or modified as they are expected to be consistent across all product monographs; however, subsection headings should be included only where applicable.

The following statement should be included at the top of the Table of Contents:

> *Sections or subsections that are not applicable at the time of authorization are not listed.*

Presentation: see template

Following the Table of Contents, for biosimilar biologic drugs (hereafter referred to as biosimilars), include the following statement:

> *[Biosimilar brand name (proper name)] is a biosimilar biologic drug (biosimilar) to [Reference biologic drug brand name].*

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

The indications listed are based on substantial evidence of the drug product's efficacy and safety, derived from adequately designed and conducted clinical studies. Only those indications authorized by Health Canada can be listed. An indication should specifically refer to the disease(s), medical condition(s) or prophylactic measure(s) the drug is authorized to treat or manage and include the patient population that the drug is intended to treat or manage (e.g., patients with atrial fibrillation, pediatrics).

Only those diagnostic test kits that have been licensed for sale by Health Canada can be named in this section. Any relevant information about the kit should be included in the Clinical Trials section.

If the drug product is indicated for use in combination with another drug product, the other drug should be referred to by its proper or common name.

Where applicable, a statement should be included to indicate that the drug product is authorized for use as an adjunct to other forms of management of the condition (e.g., lifestyle modification with osteoporosis).

When appropriate, this section should also describe the optimal use of the drug and the limitations of usefulness.

When the genotype of the patient or that of an infectious agent will affect the treatment outcome, relevant information should also be included in this section.

If the drug is controlled, the schedule by which it is controlled must be stated.

If there are situations where the use of this drug product is not therapeutically appropriate (e.g., maintenance versus acute therapy), this information should be included.

It is beyond the scope of the product monograph to provide information on the disease targeted by the authorized indications.

For biosimilars, Part I should be completed by importing information from the reference biologic drug's product monograph pertaining to indications to be authorized for the biosimilar. Specific differences between the biosimilar and the reference biologic drug (e.g., formulation or presentation differences) should be noted in the appropriate sections.

It is recognized that for vaccine products, a brief description of the disease may be useful. If this information is included it should be consistent with the Canadian Immunization Guide (see https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html).

Presentation: bullet list (for indications) and narrative.

1.1 Pediatrics

For indications authorized for adults in general, a statement regarding use in the pediatric population should be included. The term pediatric generally pertains to persons between birth and 18 years of age, but it is recognized that this may not apply to all drug products[3], therefore the Pediatrics subtitle should include the age upon which the pediatric recommendation is based. For example, if the clinical trials only included children from 6-12 years of age, this age range should be indicated. If pediatric patients were included on the basis of criteria other than age (e.g., by weight), this should be reflected here instead. One of the following or similar statements should be used:

> *Pediatrics (age range): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [Brand name] in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. [Include cross-reference to relevant sections.]*
>
> or
>
> *Pediatrics (age range): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.*
>
> or
>
> *Pediatrics (age range): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [Brand name] in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. [Include cross-reference to relevant sections.]*

Only information relating to clinical studies that directly supports the Health Canada authorized indication(s) should be included in 14 CLINICAL TRIALS.

1.2 Geriatrics

For indications authorized for adults in general, a statement regarding use in the geriatric population may be included. The term geriatric generally pertains to persons over 65 years of age but it is recognized that this may not apply to all drug products; therefore, if applicable, the Geriatric subtitle should include the age upon which the geriatric recommendation is based. One of the following or similar statements may be used:

> *Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.*
>
> or
>
> *Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.*

2 CONTRAINDICATIONS

This section should describe absolute contraindications, meaning those situations in which the drug should not be used because the risk outweighs any potential therapeutic benefit.

For contraindicated drug-drug or drug-food interactions include a brief statement with a cross-reference to the detailed information in 9 DRUG INTERACTIONS. For example:

> *[Proper name] is contraindicated with co-administration of [Drug X] as it may result in increased concentrations of [Drug X] due to inhibition of CYP3A, which may lead to QT interval prolongation and torsades de pointes. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS*

For hypersensitivity reactions, the following or similar statement should be used:

> *[Proper name] is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.*

Presentation: bullets

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Clinically significant or serious (e.g., life-threatening) safety hazards when taking the drug should be highlighted in the Serious Warnings and Precautions Box. Information for the Serious Warnings and Precautions Box may be drawn from any section of the product monograph and will be determined in consultation with Health Canada. Information related to clinically significant or life-threatening product class-related adverse reactions should also be included, if applicable, with a cross-reference to 8 ADVERSE REACTIONS. If there are no serious warnings or precautions, this box is omitted, along with the heading 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

A brief statement is provided in the Serious Warnings and Precautions Box with a cross-reference to the appropriate section of the product monograph where complete details are provided. The text in the box should generally not exceed 20 lines.

For all radiopharmaceuticals the Serious Warnings and Precautions Box should contain the following or similar statement:

> *Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.*

The Serious Warnings and Precautions Box is to be located immediately following 2 CONTRAINDICATIONS. Include the following or similar statement in 7 WARNINGS AND PRECAUTIONS section:

> *Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX*

Presentation: bullets

4 DOSAGE AND ADMINISTRATION

Biosimilar specific properties should be considered, such as potentially allergenic product container materials or differences in product presentation that require biosimilar-specific administration directions and storage conditions (include cross-reference to 11 STORAGE, STABILITY AND DISPOSAL as necessary).

4.1 Dosing considerations

Briefly list safety issues to consider when developing a dosage regimen in an individual patient (e.g., renal or hepatic disease, age, concomitant therapy, genetic polymorphism, titration, changing from intravenous to oral therapy, lab values prior to infusion, rule out pregnancy prior to administration, pre-medication is required, duration of effect, imaging time post-injection). Where different dosage forms are available, if the dosages are not equivalent the conversion value should be stated (e.g., changing from intravenous to oral therapy where a ratio other than 1:1 exists).

Identify any safety monitoring procedures that should be implemented before initiating or during therapy to facilitate the safe administration of the drug (e.g., stop drug, adjust dosage, delay additional course) and include steps that should be taken to prevent or mitigate clinically significant adverse reactions identified in 7 WARNINGS AND PRECAUTIONS.

Presentation: bullets

4.2 Recommended dose and dosage adjustment

Provide detailed and practical information on the recommended dosage. Information should include: dosage schedules, the initial dose, the optimal method of titrating dosage, the dosage range, maximum daily dose, maintenance dosage, duration of treatment and drug discontinuance. For drugs with multiple indications, dosage information should be clearly provided for each indication, route of administration and dosage form.

Guidance should be given on the dosage adjustments necessary when administering the drug in special populations for whom the product is indicated (e.g., pediatrics, geriatrics) or in the presence of pathologies (e.g., renal disease, hepatic disease, genetic polymorphism). When an age descriptor is used (e.g., pediatrics, geriatrics), the age range should be specified. In the absence of a Health Canada authorized pediatric indication, this subsection should emphasize that the product is not indicated in the pediatric population. The following or similar statement should be used:

> *Health Canada has not authorized an indication for pediatric use.* [Include cross-reference to relevant sections, if applicable.]

If no dosage adjustments are required a statement to that effect should be included, e.g.,

> *No dosage adjustment required in hepatic or renal impairment.*

Presentation: narrative

4.3 Reconstitution

Oral Solutions

This information is essential for all drug products that require reconstitution prior to administration, and should list all recommended diluents for reconstitution.

Directions for reconstitution should include the volume and type of diluents to be added and the approximate volume and concentration of the resulting product.

The recommended storage period and conditions for each solution should be stated (include cross-reference to 11 STORAGE, STABILITY AND DISPOSAL).

Presentation: narrative and/or table

Parenteral Products

For parenteral drugs requiring reconstitution or dilution before use, the relevant information should be presented in a table under subheadings of the recommended routes of administration. The recommended diluent for each proposed route of administration should also be included under each subheading. A reconstitution table should include the following four columns:

- vial size;
- volume of diluent to be added to vial;
- approximate available volume;
- concentration per millilitre.

For intravenous use, information should be separately described for:

- direct intravenous injection;
- intermittent intravenous infusion; and
- continuous intravenous infusion.

Any specific precautions should be specified below the table. For infusions, all common intravenous infusion fluids with which the drug has been shown to be incompatible, and the method of preparing the dilutions, use of in-line filters, should be listed.

The recommended storage period and conditions for each preparation, including after reconstitution, should be stated (include cross-reference to 11 STORAGE, STABILITY AND DISPOSAL).

Presentation: table and narrative (see template).

4.4 Administration

This subsection should include details concerning the methods of administration, particularly for parenteral products or for other unique formulations such as inhalation devices, implants, and transdermal formulations. Where aseptic techniques are required, this information should be included.

Use in combination with other drugs (e.g., in same intravenous solution) should also be described. Special considerations for administering the drug with respect to the formulation should be specified (e.g., do not crush, do not split if scored, capsule contents can be sprinkled). For parenteral products or those with other unique formulations, details of the administration technique for each route should be given, including use in infusion or lavages, etc.

The time of day for optimal drug effect should be indicated (e.g., evening, morning) where applicable. Timing of administration of a dose with respect to food should be indicated using the following or similar statements:

- Empty stomach, 1 hour before or 2 hours after meals;
- Before meals, usually 15 to 30 minutes before meals;
- Empty stomach preferably, may be taken with food if gastric upset occurs;
- With or without food, may be given without regard to meals;

For radiopharmaceutical products, information concerning dilutions, delivery systems, radioactivity measurement, routes of administration of the dosage form, and specific techniques should be included. The radioactivity content of all radiopharmaceuticals and patient doses should be measured and the following or similar statement should be included:

> *The patient dose should be measured by a suitable radioactive dose calibration system prior to administration.*

It is understood that there may be situations such as soft beta-emitting radioisotope labelled products, where it is not possible to measure the patient dose, and therefore the above statement is not required.

The appearance, pH and radiochemical purity of the radiopharmaceutical product should be determined prior to administration to the patient.

The manufacturer's specification for appearance, pH, radiochemical purity, chemical/radiochemical impurity, total radioactivity, specific activity, radioactive concentration, osmolality, particle size, if applicable, should be stated, along with suggested methodologies to ensure quality control results.

Presentation: narrative and/or table

4.5 Missed dose

Provide guidance on the actions to be taken in the event that a patient misses a dose.

Presentation: narrative

4.6 Image acquisition and interpretation

This subsection applies to radiopharmaceuticals. Provide the specific requirements for image acquisition and interpretation such as type of equipment and calibration scanning or imaging time post injection, location of views, and frequency of images.

4.7 Instructions for preparation and use

For radiopharmaceuticals, include detailed instructions on preparation from kits and instructions for elution process from Generators. The following or similar statement should be included:

> *The components of the reagent vial are sterile and nonpyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic technique.*
>
> *Use aseptic technique and wear waterproof gloves throughout the entire preparation procedure.*
>
> *Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.*

4.8 Radiation dosimetry

This section applies to radiopharmaceuticals. Include established radiation dose estimates absorbed by organs/tissues of an average adult human after the administration of the recommended amount (activity) of the radiopharmaceutical. The route of administration should be specified and the data presented in tabular format. All target organs and organs at risk should be included. Absorbed radiation dose estimates should be expressed in mGy/MBq (rad/mCi) per unit activity injected and/or per maximum recommended dose. The method of calculation (including parameters and models) should be specified. Dose estimates from any radiocontaminant should be provided either as a separate dose or expressed as a percentage of total dose estimates. The Effective Dose Equivalent (E.D.E) and/or the Effective Dose (E.D.) expressed as mSv/MBq (rem/mCi) should be included in the table of dose estimates.

Final Dose Estimated (the model and method of calculation should be specified).

Presentation: table (see template)

5 OVERDOSAGE

This section is meant to alert the health professional to signs and symptoms of overdose, including with acute and/or long-term drug use, and what to do in the event that an overdose occurs. Include the following information:

- a description of the acute and/or long-term signs and symptoms of overdose,
- potential sequelae/complications which may occur with the drug e.g. organ toxicity,
- current recommended management of overdosage (e.g., monitoring, use of agonist/antagonist/antidotes, method to increase elimination and/or other clinical interventions), and
- procedures that, by experience with this or similar type drugs, are known or reasonably expected to be unnecessary or unsuitable (e.g., those that may be hazardous to the patient).

Only if human data are unavailable, appropriate animal and *in vitro* data may be included.

Consider special populations (i.e., geriatric, pediatric, hepatic impairment) for which product strength (including ingestion of only one dose unit) can cause fatal poisoning; the human lethal dose (if available); and the maximum dose reported with recovery, with or without residual damage. For example:

> *Frequently observed signs and symptoms of overdose are nausea, vomiting, anemia and nephrotoxicity.*
>
> *No specific antidote exists. Discontinue therapy immediately. Hemodialysis may be indicated.*

Presentation: narrative

The following boxed statement is to be added at the end of 5 OVERDOSAGE section:

> *For management of a suspected drug overdose, contact your regional poison control centre.*

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Include the following information in a summary table at the beginning of this section:

- all authorized dosage forms, and strengths of each form in terms of the concentration of medicinal ingredient (e.g., suspension/50 mcg [micrograms] per metered spray)
- all authorized dosage forms, and strengths of each form in terms of strength of the medicinal ingredient (e.g., tablet/50 mg (as 52.5 mg as salt)
- the recommended route of administration for each form
- where applicable, the composition (e.g., components making up the capsule shell, coating, patch) should also be included for each strength of each dosage form
- a qualitative, alphabetical listing of all non-medicinal ingredients.

The terminology for the route of administration, dosage form, units of measure and packaging types will be in accordance with those published by Health Canada.

Different strengths of the product containing identical ingredients should be grouped together whenever possible. Different strengths containing different ingredients should be listed on a separate line.

To help ensure the traceability of **biologic products**, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

To help ensure the traceability of **vaccines** for patient immunization record-keeping as well as safety monitoring, health professionals should record the time and date of administration, quantity of administered dose (if applicable), anatomical site and route of administration, brand name and generic name of the vaccine, the product lot number and expiry date.

Presentation: table (see template)

A complete description of each authorized dosage form's physical characteristics should be provided, including identifiable markings. Other items such as those required for administration or quality control, reconstitution, elution etc. should also be included.

Other unique formulation information should be included in this section (e.g., inert components remain intact after elimination).

A description of the type and size of all authorized packaging formats should be included (e.g., "supplied in bottles of 100's, 500's, and 1,000's and in blister packs of 100's"). Any additional packaging information (e.g., latex), or potential for cross-contamination during manufacturing that may impact patient safety should be described (e.g., peanuts, gluten).

Presentation: narrative

Description

For biosimilars only, otherwise delete this subheading. Include a narrative description of the biosimilar biologic drug that is similar to the narrative in the reference biologic drug monograph. Incorporate changes as necessary where there are descriptive differences between the biosimilar and the reference biologic drug due to, for example, differences in formulation.

Presentation: narrative

6.1 Physical characteristics

For radiopharmaceuticals only, otherwise delete this subheading. Include a brief description of physical characteristics including physical half-life, principle radiation emission data and physical decay chart (in tabular format). For Generators the physical characteristics data for both the parent and the daughter radionuclides should be provided. Further and more detailed information (e.g., pH, particle size) should appear in 13 PHARMACEUTICAL INFORMATION.

Presentation: table

6.2 External radiation

For radiopharmaceuticals, this subsection should include a brief description of the external radiation for the radioisotope already present in the final product, or to be used in reconstitution process. Include the specific gamma ray constant for the radioisotope, and the radiation attenuation by lead shielding (in tabular format). For Generators, the physical decay chart for both the parent and the daughter radionuclides should be included.

Presentation: table

7 WARNINGS AND PRECAUTIONS

Include clinically significant information about all effects that may pose a hazard to the patient, as well as precautions to be exercised by the health professional, care provider, or by the patient to promote safe and effective use of the drug.

For blood products, include the following statement:

> *This product is prepared from large pools of human plasma. Thus, there is a possibility it may contain causative agents of viral or other undetermined diseases.*

Radiopharmaceuticals

For all radiopharmaceutical products a statement about the special restrictions for use should be provided to complement the information contained in the Serious Warnings and Precautions box. The following or similar statements should be included for all radiopharmaceuticals:

> *The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.*
>
> *The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.*
>
> *As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.*

For radiopharmaceutical kits the limitations of use should be provided. The following or similar statements should be included:

> *The contents of this kit are intended for use in the preparation of <product> and are not to be directly administered to the patient.*
>
> *The contents of the kit are not radioactive. However, following the addition of radionuclide (e.g., Tc 99m, In-111, Y-90, etc.), adequate shielding of the final preparation should be maintained to minimize radiation exposure to occupational workers and patients.*

For kits used in preparation of Tc 99m radiopharmaceuticals the following or similar statement should be included:

> *The Tc 99m labelling reactions involved depend on maintaining the tin (stannous ion) in the reduced state. Hence, sodium pertechnetate Tc 99m containing oxidants should not be employed.*

General

Subheadings should be used to group the information in this section. Subheadings should be alphabetically ordered as presented below, and only used where applicable.

For a particular subheading, if there are no effects that may pose a hazard to the patient or precautions to be exercised by the health professional, care provider or patient to promote safe and effective use of the drug, then the subheading should be omitted.

Additional subheadings may also be used. Information presented within subheadings should be in decreasing order of importance.

Include information that does not fall under the subheadings listed below.

For products derived from plasma, the inherent risks of the product should be explained. The following or similar statement should be used:

> *Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. (Include those viral reduction measures that apply to the product.) Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.*

Carcinogenesis and Mutagenesis

Include only human data where there is evidence that the drug is carcinogenic or mutagenic. Where there is only animal data, a cross-reference to the animal data in 16 NON-CLINICAL TOXICOLOGY should be provided.

Cardiovascular

Includes QTc interval prolongation. Include a cross reference to 10.2 Pharmacodynamics where applicable.

Contamination (for radiopharmaceuticals)

Include practical information for the patient to minimize the contamination potential after receiving the drug. This information must also appear in the Patient Medication Information. The following information should be provided to the patient when applicable:

> *The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Toilet should be flushed several times after use. If blood or urine gets onto clothing such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.*
>
> *Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.*

Dependence/Tolerance

Include effects resulting from both physical and psychological dependence. The amount of drug, duration of time taking the drug and characteristics of the dependence and withdrawal should be described. Treatment of the effects of the dependence should be provided.

Driving and Operating Machinery

Include any effects that may impair performance of a task requiring attention, including driving and operating machinery, along with the following or similar statement:

> *Exercise caution when driving or operating a vehicle or potentially dangerous machinery.*

Ear/Nose/Throat

Endocrine and Metabolism

This subheading should specify genetic polymorphism where applicable.

Gastrointestinal

Genitourinary

Hematologic

Hepatic/Biliary/Pancreatic

When possible, idiopathic versus metabolic liver failure should be described.

Immune

Include effects resulting from altered immune reactivity, clinically expressed as either immune activation, reactivation or immune suppression.

Immunogenicity or allergenicity should be given special consideration if applicable.

Monitoring and Laboratory Tests

Include important monitoring parameters (e.g., blood pressure), observations, laboratory or other tests required to monitor response to therapy and possible adverse reactions. The frequency of monitoring before, during and after therapy should be included. Information regarding the range of normal and abnormal values expected in a particular situation should be provided. Appropriate response to particular laboratory values should be included.

Musculoskeletal

Include information related to inflammatory rheumatic or musculoskeletal events.

Neurologic

Ophthalmologic

Peri-Operative Considerations

Include information on management before, during and after surgery. Practical details on drug discontinuation or dosage adjustment should be provided.

Psychiatric

Behavioural changes, or potentials (e.g., suicidal ideation) should be stated.

Renal

Reproductive Health: Female and Male Potential

Cross-reference to other relevant sections (e.g., 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women); include information on contraception for both females and males.

Fertility

A summary of relevant information on effects of the drug on fertility from animal or human exposure should be included under this subheading. Where there is absence of information, clearly state that no data exist.

Function

Include effects on sexual desire, erection, orgasm and ejaculation.

Teratogenic Risk

Teratogenic and nonteratogenic effects on the fetus should be included. If contraindicated in pregnancy, this should be stated in 2 CONTRAINDICATIONS.

Respiratory

Sensitivity/Resistance

Skin

Information on local reactions to vaccination administration should be described here. Where applicable, human photosensitivity (photoallergic or phototoxic) reactions should be included. Where there is only non-clinical data, a cross-reference to the 16 NON-CLINICAL TOXICOLOGY should be provided.

7.1 Special populations

7.1.1 Pregnant women

Include information related to Pregnancy Registries. The availability of a pregnancy exposure registry should also be included in the Patient Medication Information. If information on birth defects and miscarriage is available for the patient population for whom the drug is indicated, it must also be included.

The type of data should be briefly stated (human or animal) and the recommendation (e.g., avoid in a particular trimester) for prescribing the drug safely should be provided.

Teratogenic and nonteratogenic effects on the embryo/fetus/neonate should be included (e.g., withdrawal symptoms, or hypoglycemia). If contraindicated in pregnancy, this should be included here and cross-referenced to 2 CONTRAINDICATIONS. Include the following information, when available:

- Disease-associated maternal and/or fetal risk
- Maternal adverse reactions
- Embryo/Fetal/Neonatal adverse reactions
- Labour and/or delivery

Include a cross-reference to 4 DOSAGE AND ADMINISTRATION when dose adjustments during pregnancy and the postpartum period are required.

The extent of exposure in pregnancy during clinical trials should be included:

> Wide: >1,000 pregnancies;
>
> Limited: <1,000 pregnancies[4];
>
> Very Limited: individual cases only;
>
> No experience.

It should be indicated when the drug is not absorbed systemically and not known to have potential for indirect harm to the fetus.

For radiopharmaceutical use during pregnancy, the following or similar statement should be included:

> *Ideally, examinations using radiopharmaceuticals, especially those elective in nature of women of childbearing capability, should be performed during the first ten days following the onset of menses, or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.*

7.1.2 Breast-feeding

Where a drug is absorbed systemically, information about the excretion of the drug in human milk and effects on the nursing infant should be included. Adverse reactions expected in the infant should be provided and suggested measures to avoid high level exposure to the infant should be presented. The potential for serious adverse reactions or tumourgenicity should be clearly stated.

In the absence of human data, pertinent animal data should be included (e.g., adverse reactions, concentration detected in the milk plasma ratio) and the following or similar statement should be used:

> *It is unknown if [Brand name] [product] is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.*

For radiopharmaceutical administration, unless studies have shown that the product is not excreted in human breast milk, the following or similar statement should be included:

> *Where an assessment of the risk to benefit ratio suggests the use of this product in nursing mothers, formula feeding should be substituted for breast feeding.*

7.1.3 Pediatrics

Specific monitoring and hazards associated with pediatric administration of the drug should be included. The term pediatric generally pertains to persons between birth and 18 years of age, but it is recognized that this may not apply to all products[5]; therefore, the Pediatrics subtitle should include the age upon which the pediatric recommendation is based. For example, , if the clinical trials only included children from 6-12 years of age, this age range should be indicated. If pediatric patients were included on the basis of criteria other than age (e.g., by weight), this should be reflected.

In the absence of a Health Canada authorized pediatric indication, this subsection should repeat that the product is not indicated in the pediatric population, and the following statement should be used:

> *Pediatrics (age range): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.*
>
> or
>
> *Pediatrics (age range): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [Brand name] in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. [Include cross-reference to relevant sections.]*

Information about specific known safety risks associated with use of the product in the pediatric population should be reflected here (regardless of indication status), indicating the age range impacted, when known. Warnings should focus on events which are different from, or more severe than those seen in adults. An accompanying statement should explain that warnings applicable to adults are also relevant to pediatric use.

Presentation of short-term versus long term exposure warnings may be relevant, if there are differences. References to long-term exposure should be quantified (e.g., 52-week trial).

7.1.4 Geriatrics

Address specific monitoring required and hazards associated with administration of the drug in geriatric populations. Cross-reference to renal and hepatic subheadings where appropriate. The term geriatric generally pertains to persons over 65 years of age but it is recognized that this may not apply to all products, therefore the Geriatrics subtitle should include the age upon which the geriatric recommendation is based.

8 ADVERSE REACTIONS

Definitions and Terminology

The application of the Adverse Reaction section of the guidance depends in part on the interpretation of the following terms: “adverse reaction”, “adverse event”, and “serious adverse reaction”.

“Adverse reaction”, for the purpose of this guidance, is an unintended event, reasonably associated with the use of a drug and conforms to the regulatory definition of “adverse drug reaction[6]”.

An “adverse event”, for the purpose of this guidance, does not necessarily have a causal relationship to the drug. If there is any reason to suspect the event is related to the use of a drug, the event is likely an adverse reaction.

A “serious adverse reaction”, for the purpose of this guidance conforms to the regulatory definition of “serious adverse drug reaction[6]”.

See the Glossary section for more detailed definitions.

Medical Dictionary for Regulatory Activities (MedDRA)

MedDRA (www.meddra.org) should be used as the preferred terminology to describe adverse reactions. This will be at the Preferred Term (PT) Level, although there may be instances where the use of a Lowest Level Term (LLT) or a High Level Term (HLT) may be appropriate. Indicate the version of MedDRA used for the data described.

Adverse reactions that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) or disease pathophysiology in more than one body system (e.g., congestive heart failure, nocturnal dyspnea, angina, pedal edema) should be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect.

Council for International Organizations of Medical Science (CIOMS)

The standard for defining frequency terms will be based on the CIOMS convention as indicated below:

Very common: ≥1/10 (≥10%);

Common (frequent): ≥1/100 and <1/10 (≥1% and <10%);

Uncommon (infrequent): ≥1/1,000 and <1/100 (≥0.1% and <1%);

Rare: ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%);

Very rare: <1/10,000 (<0.01%), including isolated reports.

General Information

The Adverse Reaction section contains information on adverse reactions identified during clinical trials and post-market surveillance. Information relating to clinical trial adverse reactions and post-market adverse reactions should be presented separately, in a clear and logical manner and be included in a table where possible. The information to be included will be determined in consultation with Health Canada.

The following factors may be considered for the inclusion of adverse reactions:

- frequency of reporting;
- frequency exceeds that of placebo or control;
- evidence of dose-response;
- time relationship and evidence of de-challenge or re-challenge;
- consistency with pharmacology of the drug;
- class effect;
- serious events including those rarely seen and that occur generally in association with drug therapy. These adverse reactions should be listed even if there are only one or two reported events, unless it is clear that a causal relationship can be excluded. Examples include:
    - liver failure;
    - agranulocytosis;
    - rhabdomyolysis;
    - idiopathic thrombocytopenic purpura;
    - intussusception;
    - hypersensitivity.

In addition, the adverse reactions for vaccines should be broken down by age of patient and should draw out relevant Canadian clinical experience.

Inclusion of events that are infrequent and minor, typically observed in the absence of drug therapy, or not plausibly related to the drug should be avoided. Note that at this time there are no universally accepted algorithms to assess causality in support of converting adverse events to adverse reactions. Results of significance testing should be omitted unless they provide useful information and are based on a pre-specified hypothesis in an adequately designed study.

For biosimilars, the adverse drug reaction information in the following subsections should be identical to that in the reference biologic drug product monograph (including narratives and tables) except that only adverse reaction information that is relevant to indications authorized for the biosimilar should be included. Include the following statement:

> *The adverse drug reaction profiles reported in clinical studies that compared [Biosimilar brand name] to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.*

8.1 Adverse reaction overview

Summarise the adverse reaction information that would be most useful to the health professional that may affect prescribing decisions or would be useful in observing, monitoring or advising care providers and/or patients.

Provide information on the most serious and/or most frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. Frequencies should be stated as accurately as possible. It should not be a summary of the safety database.

The serious and/or unexpected adverse reactions described in other sections of the product monograph should be cross-referenced here. Avoid subjective terms (e.g., well-tolerated) since they are non-specific, promotional and/or poorly defined. The most serious and/or most frequently occurring adverse reactions may be described as follows:

> *The most commonly reported adverse reactions [specify in adults / pediatric patients with age range] are nausea (34%), vomiting (22%), diarrhea (18%), and febrile neutropenia (0.4%).*

A cross-reference to 7 WARNINGS AND PRECAUTIONS should be made where there are measures to be taken to avoid specific adverse reactions, or measures to be taken if specific reactions occur.

For combination products, include a statement at the beginning of this section pointing out which particular adverse reactions are usually attributed to which active substance of the combination, where known.

This subsection should highlight the following:

1. Serious adverse reactions;
2. The most frequent adverse reactions (e.g., those occurring at a rate of 10% or greater);
3. Adverse reactions that most commonly result in clinical intervention such as:
   - discontinuation;
   - dose modification;
   - concomitant medication to treat an adverse reaction symptom;
   - close monitoring;
4. Factors that may affect the rate or severity of a reaction:
   - disease state;
   - concomitant therapy;
   - demographic subgroup;
   - dose;
   - duration of therapy (e.g., adverse reactions that appear in the beginning of treatment but usually resolve with continuous treatment, or adverse reactions that may only appear with longer term treatment);
5. In some cases it may be appropriate to list the serious adverse reactions that are typical for the drug class, but have not been specifically observed in the clinical trials with this particular drug.

Presentation: narrative

8.2 Clinical trial adverse reactions

General Statement

To provide a common understanding when interpreting adverse reaction data from all clinical trials, the following or similar introductory statement should be used:

> *Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.*

Separate tables may be required for different indications (e.g., oncology and a non-oncology indication) or different formulations (e.g., oral, intravenous) or different drug combinations.

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

8.2.1 Clinical trial adverse reactions – pediatrics

Adverse reactions observed in pediatric studies that directly support authorized indications for use in pediatric populations should focus on reactions that are more frequent, more severe, or different from those observed in adults. An accompanying statement should explain that reactions applicable to adults are also relevant. Presentation of short-term versus long-term exposure warnings may be relevant, if there are differences. In this context, extensive tables of adverse reactions should not be presented. A text description of clinically relevant reactions is preferred.

In the absence of a Health Canada authorized pediatric indication, and only where there are important safety differences between adults and children, a brief statement should be presented on observed clinical trial adverse reactions.

If relevant, include and describe: age characteristics, any clinically relevant differences (i.e., seriousness or reversibility of adverse reaction) between safety profiles in adult and pediatric populations, or any relevant age groups, uncertainties due to limited experience. If the observed safety profile is consistent between children and adults this could be stated.

Presentation: narrative

Description of Data Sources

The presentation of adverse reaction data should be preceded by a clear, brief, description of the data source. Information should include overall exposure (e.g., number of patients, dose, schedule, duration of treatment), patient population, demographics, and a brief description of the study design (e.g., placebo-controlled, active-controlled), composition of control group, any critical exclusions, and any other relevant information.

Relative Frequency of Adverse Reactions

The frequency of a particular adverse reaction should be derived from all treatment-emergent adverse events, independent of the investigator's opinion on the relationship to the study drug.

Whether comparator data would be included or not in this subsection of the product monograph, should be based on consultation with Health Canada.

Common and very common adverse reactions (those with frequency rates ≥ 1%) should be presented in a table. The frequency cut-off for the listing of common adverse reactions identified from clinical trials should be appropriate to the size and composition of the safety database and should be determined in consultation with Health Canada. The frequency cut-off should be noted in the table header and the text accompanying the table.

A single table is preferable. Multiple tables are appropriate when the drug's adverse reaction profile differs substantially from one setting to another. The content of the additional tables should be limited to only those adverse reactions for which there were meaningful differences in rates. Important differences may result from:

- different product indications;
- formulations;
- population subgroups;
- study durations;
- dosing regimens;
- types of studies (e.g., intensely monitored versus a large outcome study).

Data in the primary adverse reactions table should be derived from clinical trials submitted in support of the proposed indication.

The table should indicate:

- patient population from which the data was derived;
- dose and dose regimens used (fixed or flexible, up-titration, etc.);
- duration of the treatment period;
- basis for inclusion in the table (e.g., all adverse reactions at incidences above a threshold and higher than in the placebo or control group);
- data source used to derive the frequencies (e.g., treatment-emergent adverse events);
- number and percentage of patients in each treatment group.

Frequencies should generally be rounded off to the nearest integer. An exception would be for particularly serious adverse reactions occurring at low frequencies in a large study where fractions of a percent may be meaningful.

Information should be categorized by system organ class (SOC) proposed by MedDRA according to the following hierarchal structure:

1st - by SOC in alphabetical order;

2nd - then by decreasing frequency within each SOC.

Where relevant, adverse reactions due to drug discontinuation should be presented separately and the method used to collect the data should be indicated (e.g., voluntary reporting or applied questionnaire).

The data table should be followed by a brief narrative to supplement the information in the table and include where applicable, the following:

- **Dose-response information:** identify adverse reactions that exhibit a dose-response and describe the manner in which dose-response was investigated.
- **Special Populations:** information about observed differences in adverse reaction rates in various demographic groups or disease subsets.
- Information on dosage and duration of therapy linked to adverse reactions.

Presentation: table and narrative (see template). Graphs should not be used to present adverse reaction information.

8.3 Less common clinical trial adverse reactions

Present clinical trial adverse reactions with a frequency below the specific cut-off for inclusion in the table of common and very common adverse reactions. The less common adverse reactions should be presented as a listing and categorized by SOC, alphabetically.

Generally, one list of less common reactions is presented, with pooled data including controlled and uncontrolled trials relevant for the characterisation of safety for the authorized indications, unless there are major differences between studies or populations.

Presentation: list

8.3.1 Less common clinical trial adverse reactions – pediatrics

Apply the same approach used to present adult data in 8.3 Less Common Clinical Trial Adverse Reactions.

Presentation: table and narrative. Graphs should not be used to present adverse reaction information.

8.4 Abnormal laboratory findings: hematologic, clinical chemistry and other quantitative data

Clinically significant changes in laboratory findings identified during clinical trials should be summarized in table format. Where applicable, there should be one table for hematologic changes, one for chemistry changes, and one for quantitative data (e.g., electrocardiograms). The laboratory parameters should be listed in alphabetical order. The table should define the magnitude of change from normal values that was considered clinically relevant, and the number of patients and percentage of the population that met the criteria.

Presentation: table

Clinical Trial Findings

Outline any differences between adults, geriatrics and pediatrics as necessary with regard to abnormal laboratory findings.

Post-Market Findings

Outline any differences between adults and pediatrics as necessary with regard to post-market abnormal laboratory findings.

8.5 Post-market adverse reactions

This subsection should include Canadian and international post-market adverse reactions including serious and/or unexpected adverse reactions that are reported through post-market surveillance and/or identified in Phase IV clinical trials. For guidance relating to the determination of serious adverse reactions and further information, please refer to the Health Canada Guidance Document for Industry - Reporting Adverse Reactions to Marketed Health Products.

The following factors may be considered for the inclusion of post-market adverse reactions:

- seriousness of event;
- number of reports;
- strength of causal relationship;
- new events;
- increase in severity and/or frequency over adverse reactions observed in clinical trials;
- class effect.

Adverse reactions already listed in the Clinical Trial Adverse Reactions section should not be repeated in this section unless there are changes in severity, frequency or character.

All relevant sections affected by new safety information should be updated according to the most recent available safety data from Phase IV clinical trials or spontaneous reports for the drug, or according to product monograph updates in the drug class.

Presentation: Narrative. If the volume warrants, the information should be presented in a table using the same format as Clinical Trial Adverse Reactions.

9 DRUG INTERACTIONS

9.1 Serious drug interactions

Serious (e.g., life-threatening) interactions should be included in a brief boxed statement, with a cross-reference to detailed information in 9.4 Drug-Drug Interactions. If a drug interaction is included in 2 CONTRAINDICATIONS or 3 SERIOUS WARNINGS AND PRECAUTIONS BOX it must also be included in this box. Text should not exceed 20 lines.

In the absence of a serious drug interaction at the time of authorization, this box is omitted, along with the heading 9.1 Serious Drug Interactions

Presentation: bullet form within a box (see template)

9.2 Drug interactions overview

Potential interactions should be presented in the Overview subsection. This would include interactions suspected based on the pharmacokinetic or pharmacological profile of the drug (e.g., cytochrome P450 interactions, QT interval prolongation potential, genetic polymorphism).

This information should be presented in narrative format. A brief statement about the potential mechanism of the potential interaction should be presented.

Drug class statements should appear here if the interaction has not yet been documented but would be clinically relevant. When a potential drug class interaction is considered clinically relevant, representative drugs from that class should be added to the drug interactions table.

The information is to be based on clinical relevance and will be determined in consultation with Health Canada.

Any potential interaction with alcohol should be discussed briefly, with more information provided in 9.3 Drug-Behavioural Interactions.

Include practical guidance for the prevention or management of drug interactions. The mechanism of the interaction should be briefly stated.

Presentation: narrative

9.3 Drug-behavioural interactions

Briefly present potential interactions in terms of individual behavioural risks including, but not limited to, alcohol consumption, sexual activity, and smoking, which may result in unfavourable adverse events or treatment outcomes.

Presentation: narrative

9.4 Drug-drug interactions

All clinically relevant drug-drug interactions (including those only supported by animal or *in vitro* studies) should be presented.

Pharmacokinetic studies presenting information regarding the kinetics of specific drug combinations should be presented here. The following or similar statement should be included before the table:

> *The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).*

Where no interaction data is known the following or similar statement should be included:

> *Interactions with other drugs have not been established*.

Presentation: table format. Where data is limited, the information may be better presented in narrative format. The table should list the proper (or common) name of the drugs, the source of evidence for the interaction (e.g., case study, clinical trial or theoretical), the effect and a clinical comment. See the template for an example of a drug- drug interaction table.

9.5 Drug-food interactions

Briefly present known or potential interactions with food or beverages (e.g., grapefruit juice, caffeine) and practical guidance for the health professional. The composition of a meal should be described when this may affect the pharmacokinetics (e.g., high fat content meals) of the drug product. Cross-referencing to 4 DOSAGE AND ADMINISTRATION may be required when the timing of food consumption with respect to drug administration could avoid or worsen the interaction. Interactions caused by different formulations of the drug should also be indicated.

Where no interaction data is known, the following or similar statement should be included:

Interactions with food have not been established.

Presentation: narrative.

9.6 Drug-herb interactions

Briefly present known or potential interactions with herbal products and practical guidance for the health professional.

Where no interaction data is known, the following or similar statement should be included:

Interactions with herbal products have not been established.

Presentation: narrative.

9.7 Drug-laboratory test interactions

Briefly present laboratory tests affected by the presence of the drug, such as interfering with the accuracy of the test results or methods (e.g., antihistamines diminish the positive reactions to dermal reactivity indicators). Practical guidance for the health professional should be included.

Where no interaction data is known, the following or similar statement should be included:

Interactions with laboratory tests have not been established.

Presentation: narrative.

10 CLINICAL PHARMACOLOGY

This section should include a concise synopsis of the salient features of the drug's mechanisms of action, pharmacodynamics and pharmacokinetics. The information should have a demonstrated relevance to the safe and effective use of the drug in humans. Relevant animal data (e.g., safety pharmacology) should be included only where human studies are lacking or deficient, or where the information is relevant to interpretation of toxicity or mode of action.

For biosimilars, comparative pharmacokinetic/pharmacodynamic (PK/PD) data from the biosimilar program should not be presented in this section. Biosimilar data should be presented in Part II: Scientific Information, 14 CLINICAL TRIALS.

10.1 Mechanism of action

Briefly describe the established mechanism through which the drug produces its pharmacologic effects for both the therapeutic action and the drug toxicity. The mechanism of action should be described at the cellular or receptor/enzyme level and in relation to the target organs and the whole body, depending on what is known. If the mechanism of action in relation to the therapeutic effects is unknown, this should be stated.

A brief description of the disease pathophysiology may be included if it improves the understanding of the drug's pharmacology.

For anti-infective drugs, a brief description of the action of the drug against microorganisms or enzyme systems involved in replication should be included.

Presentation: narrative

10.2 Pharmacodynamics

Briefly describe the reasonably well-established therapeutic as well as unintended (toxic) effects of the drug, including active metabolites, where applicable.

The following information should be included:

- The principal pharmacodynamic effects related to the therapeutic action. Effects on mechanistically important biomarkers should be included.
- Receptor/enzyme selectivity if there is data to indicate this may be related to therapeutic action or toxicity.
- Dose response and related pharmacokinetic/pharmacodynamic (exposure/response) analyses, including the time to onset, magnitude and duration of the pharmacodynamics effects in relation to exposure.
- Pharmacologic effects relevant to safety.
- Tolerance, rebound effects, potential for abuse, dependence and withdrawal effects.
- Factors affecting pharmacodynamic effects (e.g., interactions via cytochrome P450, drug transporters, genetic polymorphism, antibody formation). This should not include drug interaction information which is presented under section 9 DRUG INTERACTIONS.
- A factual description of any effects of the drug on ECG intervals (e.g., QTc, QRS, PR) and ventricular heart rate should be provided, including dose and duration of treatment and magnitude of effect. Lack of any effect on these parameters should also be stated in the context of the exposures studied. In exceptional situations in which optimal ECG data might be lacking, a statement should be included noting this deficiency or describing the best available alternative data. These data should be presented under a separate subheading (e.g., Cardiac Electrophysiology, Electrocardiography).

Presentation: narrative

10.3 Pharmacokinetics

Include a brief statement describing whether the drug exhibits linear or non-linear pharmacokinetics. If non-linear, the nature of non-linearity, including the dose range over which the non-linearity is observed as well as the underlying mechanism of non-linearity, should be described.

A summary of the most clinically relevant pharmacokinetic parameters for the drug, including active metabolites should be presented in a table (see template). The table should include: maximum observed concentration (Cmax), area under the curve (AUC), time to maximum observed concentration (tmax), volume of distribution (Vd), elimination half-life (t1/2) and clearance (CL).

Generally, the pharmacokinetic data from a healthy population should be presented. If meaningfully different from the healthy population, the pharmacokinetic data from patient population(s) for which the drug is indicated should also be included.

The summary table should be followed by a brief explanation of the following, under appropriate subheadings.

Absorption

Bioavailability, whether absorption kinetics are linear or nonlinear over the range of doses and concentrations, food effect on absorption (even if negligible) and time to steady state.

Distribution

Degree of protein binding, sites of distribution, rate and extent of uptake by target organs if clinically relevant, and whether the drug crosses the blood-brain barrier. Placental transfer and secretion into milk should be described under 7.1 SPECIAL POPULATIONS.

Metabolism

Sites and pathways of metabolism (e.g., p-glycoprotein, cytochrome P450) and extent of first-pass metabolism, metabolites and their activity, dose dependent changes in metabolism, effect of the drug, including active metabolites, on metabolic pathways (e.g., inhibition or induction of p-glycoprotein, cytochrome P450). If these effects result in clinically relevant drug interactions, a cross-reference to 9 DRUG INTERACTIONS should be included.

Elimination

Include route(s) of excretion and the percentage of the drug, including active metabolites, excreted by each route, and the mechanisms of the excretory routes. If the drug is not excreted but eliminated by metabolism (e.g., large proteins), or if it is eliminated by both excretion and metabolism, this should be stated.

Duration of Effect

This subsection applies specifically to vaccines and should describe the duration of effect of the recommended dose (e.g., duration of detectable levels of antibodies and/or conferred immunity status). It should provide the supporting information for the dosing information, such as booster dose requirements and frequency, which is specified under 4 DOSAGE AND ADMINISTRATION.

Special Populations and Conditions

Include pharmacokinetic information that is relevant to special populations [e.g., pediatrics, geriatrics, sex, pregnancy and breast-feeding (placental transfer and secretion into milk), genetic polymorphism, ethnic origin] and certain conditions (e.g., hepatic insufficiency, renal insufficiency, obesity).

Where a pediatric indication has not been authorized by Health Canada, it may still be useful to include the results of pharmacokinetic studies in children that have been submitted to Health Canada, if these results provide useful information for the prescriber. However, the fact that a pediatric indication has not been authorized by Health Canada should be re-stated here.

Presentation: table (for pharmacokinetic values) and narrative (see template).

11 STORAGE, STABILITY AND DISPOSAL

Specify the recommended storage conditions for each dosage form. If dispensing in a particular type of container (such as a light-resistant container) is necessary, this should be stated. If a change in a physical attribute is known to occur (including colour or clarity) during storage, an appropriate warning and significance of the change should be included.

All labelled storage recommendations should be supported by appropriate stability studies.

For reconstituted products, including parenterals, the recommended storage period and conditions for each solution should be stated. In view of the potential risks from microbial contamination during preparation of parenterals that do not contain a preservative, recommended storage periods should not exceed 24 hours at room temperature (15 to 30°C) and 72 hours under refrigeration (2 to 8°C) and can be much shorter, depending on the product.

Any known incompatibilities should be stated, including incompatibilities between drugs, diluents or infusion fluids, primary packaging, or administration sets, or with any other material with which the drug may come into contact.

Disposal instructions should be included for all drug products. For those potentially hazardous drug products, include a cross-reference to more detailed safe disposal instructions under 12 SPECIAL HANDLING INSTRUCTIONS.

The following or similar statements should be included when appropriate:

Temperature:

Store under refrigeration (2 to 8°C).

Store at room temperature (15 to 30°C).

Light:

Protect from exposure to light.

Moisture:

Protect from moisture.

Protect from high humidity.

Others:

Keep out of reach and sight of children.

For radiopharmaceutical kits, the storage conditions and expiry for the kit and the reconstituted preparation should both be included. Lead shielding requirements should also be included (for example, a product should be stored upright in a lead shielded container at controlled room temperature). The following or similar statement should be used:

> *Do not use the kit beyond the expiration date stamped on the box. After preparation [product] should be stored at room temperature until administration, within [x] hours of radiolabelling.*

Presentation: narrative

12 SPECIAL HANDLING INSTRUCTIONS

Any special handling instructions and cautionary statements for anyone who is likely to come into contact with potentially hazardous products during storage, handling, preparation, administration and disposal should be clearly specified (e.g. handling by women who are pregnant or breast feeding). This is of special importance for hazardous drugs that may be mutagenic (e.g., cytotoxic drugs). When necessary, special instructions should be included for the decontamination and safe disposal of drugs and associated material (e.g., appropriate shielding of radioactive products, use of personal protective equipment (PPE), toilet should be flushed several times after use, etc.).

Presentation: narrative

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

This subsection should include information on the drug substance under the following headings:

a) Proper name or common name;
b) Chemical name;
c) Molecular formula and molecular mass;
d) Structural formula, including relative and absolute stereochemistry;
e) Relevant physicochemical properties, for example, physical description, solubility over the physiological pH range (pH 1-8), polymorphic form.
f) Pharmaceutical standard (for biologics), for example, for products expressed in international units, whenever possible, the reference standard should be specified (e.g., World Health Organisation International standard).

Product Characteristics

For radiopharmaceuticals, provide detailed information or a lengthier description of product characteristics that are in addition to those mentioned under 6.1 Physical Characteristics.

For biologics, this subsection should describe the method of manufacture. Sponsors are not expected to supply proprietary information, but they must provide enough detail to provide health professionals with an understanding of how the product is prepared.

Viral Inactivation

For products derived from plasma, the viral reduction steps should be detailed. Information on the selection criteria of donors should be provided.

14 CLINICAL TRIALS

This section of the product monograph should contain data from the main studies in support of the drug's efficacy and safety and should generally not include other information as this section is not intended to be a comprehensive reference of all studies related to the drug product.

The detailed information should address the following major components:

- study design,
- study population,
- disposition of subjects, and
- results of study endpoints that support the efficacy and safety of the drug, including estimated treatment effects and the corresponding measures of uncertainty (p-values and confidence intervals).

The information on clinical trials should be presented in a tabular format for ease of retrieval of the information. The demographic and baseline characteristics data should be presented in one table (see template) with the aggregate results provided in a separate table. In the case of different indications, age groups, etc., separate tables should be used, in order of authorization.

Include comparative bioavailability studies, as required, for revised formulation and new dosage forms.

14.1 Efficacy and safety studies

Trial Design and Study Demographics

This subsection should describe the major design characteristics of the study, including:

- type of control,
- level of blinding (e.g., double-blinded),
- how subjects were assigned to treatment groups (e.g., randomized),
- route of administration,
- treatment arms (doses administered), and
- duration of therapy.

The description of the study population should include a summary of key inclusion and exclusion criteria as well as summary statistics on baseline demographic and disease characteristics.

Endpoints used to establish the efficacy of the drug should be described. In the table displaying the study results, details regarding the statistical methods used to analyse these endpoints, including the procedures for multiplicity control, should be captured as a footnote.

Studies to be included should be carefully planned, properly designed and well conducted to directly support the indication, the efficacy, safety and dosing regimens for the drug, and provide information about the limitations of efficacy.

Studies that should not be included are those that:

- imply or suggest effectiveness for an unauthorized indication;
- present the incidence, frequency, or severity of adverse reactions and are not the subject of an acceptable NDS or SNDS submission.

The following points should be taken into consideration when an active comparator is utilised in a given clinical study:

- the active comparator should be used as indicated in its Canadian product monograph (e.g., same target population, dosage, route of administration and single or multiple drug therapy).
- for non-inferiority and equivalence studies, the selection of the comparability margin should be clearly justified.
- the comparator should be reported by its proper or common name.

For biosimilars include the following or similar statement for comparative trials:

Clinical studies conducted to support similarity between [Biosimilar brand name] and the reference biologic drug included:

- [text] [Provide a general description of study 1, for example, a randomized comparative bioavailability study performed in healthy volunteers.]

- [text] [Provide a general description of study 2, for example, a double-blind, randomized, comparative safety and efficacy study performed in patients with moderate to severe rheumatoid arthritis.]

Presentation: Table and narrative (see template)

14.2 Study results

Results of study endpoints that support the efficacy and safety of the drug, (and for biosimilars, compare the biosimilar biologic drug to the reference biologic drug) including estimated treatment effects and the corresponding measures of uncertainty such as p-values and confidence intervals while accounting for multiple testing, should be presented.

Clinically relevant results from subgroup analyses that are considered to be of particular interest could be acceptable following consultation with Health Canada, with the caveat that the results should be interpreted with caution given the inherent risks with subgroup analyses in general.

For biosimilars, there should be no claims of bioequivalence or clinical equivalence between the biosimilar and the reference biologic drug. Tabulated results should include footnotes describing any statistical method used and any applied acceptance criteria (i.e., the "equivalence margin"). For biosimilar submissions that include only comparative bioavailability studies, leave this section blank and include the following statement:

> *See 14.3 Comparative Bioavailability Studies.*

Presentation: table (see template)

14.3 Comparative bioavailability studies

For all revised formulations and new dosage forms whose safety and efficacy is supported solely on the basis of a comparative bioavailability study, a summary of the study should be provided in table format.

This table should be preceded by a narrative outlining the design of the comparative bioavailability study (i.e., single/multiple dose, fasting/fed, crossover/parallel, dose/number of dosing units, number of healthy male/female volunteers/patients). The narrative should incorporate the identities of the compared products.

For biosimilars, comparative pharmacokinetic (PK) studies should be conducted to rule out differences in PK characteristics between the biosimilar and the reference biologic drug. For clinical studies conducted to support similarity between a biosimilar and the reference biologic drug, there may be cases where a pharmacodynamic (PD) marker may be used in lieu of clinical endpoints or as additional support for similarity. If this is the case, include a brief narrative describing the study and a tabulation of the PD results including the appropriate statistical analyses.

Presentation: table and narrative (see template)

14.4 Immunogenicity

For vaccines, include information on efficacy by class of individuals, to recognize differences in immunogenicity.

For biosimilars, include comparative immunogenicity results, if applicable, with a brief narrative describing the testing strategy for anti-drug antibodies (ADA) and the overall incidence of treatment-emergent or treatment-enhanced confirmed binding antibodies.

The following or similar statements may be included:

> *Comparing the incidences of antibodies between studies or between products may be misleading due to differences in the types, sensitivities and/or specificities of the assays employed.*
>
> or
>
> *As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.*

Presentation: narrative

14.5 Clinical trials - reference biologic drug

For biosimilars only, otherwise delete this subheading. Import the clinical trial information that appears in the reference biologic drug's monograph with respect to indications to be authorized for the biosimilar. Clinical trial data for indications that will not be authorized for the biosimilar should not be included.

[text]

15 MICROBIOLOGY

This section is required for all antimicrobial drugs. It is to comprise laboratory studies and be divided, where appropriate, into *in vitro* and *in vivo* subsections. It should also contain a description of the microbiological data that supports the pathogen(s) for the authorized indication, and that supports the microbiological information summarized under section 10 CLINICAL PHARMACOLOGY.

Details regarding interpretive criteria, standards for susceptibility testing, and standards for reference pathogens, should be included (as per current acceptable standards). Information on drug resistance and cross-resistance should be included.

Presentation: table(s) and narrative

16 NON-CLINICAL TOXICOLOGY

This section should include a brief description of the non-clinical toxicology findings which are relevant for the safe use of the drug and/or contribute to the understanding of a drug's toxicological profile. It is expected that only the most relevant findings will be described in this section. For each study described, and where applicable, the species, route of administration, dosage regimen (e.g., dose levels, frequency of administration, duration of dosing, formulation), relevant findings, the No Observed (Adverse) Effect Level and/or Lowest Observed (Adverse) Effect Level, and calculated margins of exposure should be provided.

The following or similar statements should be included, where applicable:

> *No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether [Brand name] affects fertility in males or females.*
>
> *As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.*

For biologics, this section should confirm if long-term studies have been done to evaluate immunogenicity.

For biosimilars, include toxicology information that appears in the reference biologic drug product monograph. The reference biologic drug brand name should be changed to the proper name (INN). Data that relates only to indications that will not be authorized for the biosimilar should not be included.

The data should be presented in the following order under appropriate subheadings:

General Toxicology (single and repeat-dose studies)

These studies should be limited to those needed to support market authorization (for example, 6 month study in rodents, 9 month study in non-rodents[7]).

Carcinogenicity

Study results that demonstrate a drug's carcinogenic potential should be described. If a drug does not exhibit carcinogenic potential, or the carcinogenic potential has not been fully evaluated, this should be stated. Tumour findings considered relevant to the safe use of the drug should be briefly described in 7 WARNINGS AND PRECAUTIONS, with a cross-reference to the information provided here.

Genotoxicity

Study results that demonstrate a drug's genotoxic potential should be described. If no genotoxic effects are identified, or the genotoxic potential has not been fully evaluated, this should be stated, with a summary of the types of studies conducted. Findings considered relevant to the safe use of the drug should be briefly described in 7 WARNINGS AND PRECAUTIONS, with a cross-reference to the information provided here.

Reproductive and Developmental Toxicology

Only findings that are toxicologically meaningful should be described. In cases where a drug does not demonstrate reproductive and/or developmental toxicities, or the reproductive potential has not been fully evaluated, this should be stated. Findings considered relevant to the safe use of the drug should be briefly described in 7 WARNINGS AND PRECAUTIONS, with a cross-reference to the information provided here.

Special Toxicology

Studies briefly described here may include photosafety, immunotoxicity, abuse liability, combination drug toxicity, etc. Important mechanistic studies may also be included unless it is more relevant to present them under other subheadings (e.g., General Toxicology, Carcinogenicity).

Juvenile Toxicity

Where the drug is indicated or likely to be used in the pediatric population, the results from studies in juvenile animals should be presented, when available.

Presentation: Narrative where possible. Table format only if presentation will be more concise. Information should only be presented once, either in narrative or table format.

16.1 Comparative non-clinical pharmacology and toxicology

For biosimilars only, otherwise delete this subheading, as well as 16.1.1 Comparative Non-Clinical Pharmacodynamics and 16.1.2. Comparative Toxicology.

16.1.1 Comparative non-clinical pharmacodynamics

In vitro Studies

Presentation: narrative and/or table

16.1.2 Comparative toxicology

Presentation: narrative and/or table

17 SUPPORTING PRODUCT MONOGRAPHS

List only Health Canada authorized product monographs that were supportive in the development of the product monograph (e.g., Canadian Reference Product for a generic, or Reference Biologic Drug for a biosimilar biologic drug), combination product, or subsequent entry product. Where there are no such supporting product monographs, this section, including heading, should be omitted.

Presentation: numbered list as follows:

Brand name (dosage form, strength), submission control number, Product Monograph, Sponsor. (Mon DD, YYYY)

PATIENT MEDICATION INFORMATION

Introduction

The Patient Medication Information section is a plain language translation of information contained in Parts I and II of the product monograph. Plain language means using the simplest, most common words possible, so that information is clear, concise and easy to understand for the intended audience.

For the purposes of the product monograph, "patient" is defined as the general public. This may include an individual using the drug, a caregiver or someone who is simply interested in obtaining information about a drug.

The Patient Medication Information should be produced as part of the product monograph for all drugs that are required to comply with this guidance document. This applies to all drugs regardless of administration setting (e.g., hospital use only, emergency), because the ultimate audience is the general public.

The content for this section will be determined in consultation with the sponsor and Health Canada and is limited to information found in Parts I and II.

If there are other drug-specific guidelines [e.g., Basic Product Monograph Information for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), November 2006], this information should also be incorporated.

Where information is substantially different for each indication (e.g., diagnosis versus treatment/therapy), route of administration or formulation of the product, a separate Patient Medication Information section is required for each. For example, a product that is indicated for migraine and hypertension would have two Patient Medication Information sections.

Language

Recognizing that there are different audiences for this information, for consistency, the Patient Medication Information section should be written as if it will be read by an individual who will use, or be administered the drug. For drugs where the patient is not an active participant (e.g, inhaled anaesthetics or other drugs, such as radiopharmaceuticals, that are administered under special conditions), the language may be adjusted.

Health literacy levels in Canada vary significantly among regions and demographically. For this reason, Plain Language Labelling and grade 6-8 literacy levels should be utilized. Assume that the reader has no prior knowledge of the medication or how to use it. Use the simplest, shortest words possible.

It is the responsibility of the sponsor to ensure that any translations of the Patient Medication Information section accurately reflect the meaning of the original authorized version and the information in Parts I & II of the product monograph.

In developing the Patient Medication Information section, sponsors are strongly encouraged to seek help from appropriate plain language resources, including the Canadian Public Health Association and their publication Good Medicine for Seniors: Guidelines for Plain Language and Good Design in Prescription Medication[8]. The guidelines in this document show how to write health information in plain language for patients (for both prescription and non-prescription drugs), and include a compendium of plain language terminology. Sponsors would also benefit from user-testing their Patient Medication Information for comprehension.

Style guide

These style guide recommendations apply to the Patient Medication Information section of the Product Monograph as well as any patient oriented documents or leaflets that are produced as part of the drug product packaging.

- The Patient Medication Information section should not be promotional in tone or content. The text should be factual and avoid vague generalizations.
- Brand name should be used in the headings and the text.
- Page layout: left-justified.
- Margins:
  a) Patient Medication Information - 2.5 centimetre (1") top, bottom and sides
  b) Patient Medication Information leaflet - 0.75 cm (0.3") top, bottom and sides
- Font:
  a) Patient Medication Information - Sans Serif type fonts (e.g., Calibri 12 point);

b) Patient Medication Information leaflet - Sans Serif type fonts (such as Arial or Calibri) are recommended, text - 10 point and tables - 9 point. Flexibility will be exercised in those situations where a smaller font may be necessary due to packaging constraints or printing limitations. Legibility is the goal and sponsors are responsible for ensuring that the Patient Medication Information, as it appears on the leaflet, is clear and easy to read to the patient under the customary conditions of purchase and use.

   A person with normal vision, or those with corrective glasses that restore normal vision, should be able to read the information without straining. The colour, contrast, the position, and the spacing of the information are all to be taken into consideration in complying with these requirements.

- Headings and Subheadings: bold type face should be used. Italics and underlining should be avoided. All upper case font should also be avoided except where instructed (for example, major section headings like READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE, PATIENT MEDICATION INFORMATION at the beginning of the Patient Medication Information).
- The information should be as brief and succinct as the requirements of the guidelines allow.

Illustrations

Illustrations that help demonstrate the proper use of a self-administered product (e.g, inhaler, injectable products) are encouraged.

Pictures or graphics can often be misleading as to the use, merit, and character of a drug product and should be avoided. Pictograms should not be used.

Boxed Statements

When there is a boxed statement in any section of Part I or II, a corresponding boxed statement, in plain language, should appear in the relevant section of the Patient Medication Information.

Readability and Usability

To ensure the Patient Medication Information section can be understood:

- Aim for a Grade 6 to 8 reading level. Tests and resources are available in libraries and online to ensure the readability of text such as the Flesch-Kincaid, Fry Graph Readability Formula and SMOG (Simple Measure of Gobbledygook) health literacy readability tools.
- The Patient Medication Information section should be simple, clear and easy to understand so that patients are able to find, understand and act upon the information. Consider these tips:
    - Write directly to your reader, using the first person (you, we).
    - Use clear, positive instructions (e.g., **Instead of:** Do not take this medicine on an empty stomach. **Say:** Take this medicine with food.).
    - Write instructions consecutively (i.e., in the order you want them carried out).
    - Use the shortest, most common words possible (e.g., **Instead of:** You may experience edema of the legs. **Say:** Your legs may swell.).

- Avoid acronyms, abbreviations, foreign terms and technical jargon. If you must use a technical term, define it in plain language immediately after the word.
- Use active (rather than passive) voice. Make sure the subject is named and acts on the object, and keep the subject close to the verb (e.g., **Instead of:** This medication is to be taken before every meal by your child. **Say:** Give your child this medication before every meal.).
- Where possible, use bulleted information instead of sentences and paragraphs. When sentences are necessary, keep them short with one idea in each sentence. Break up long text and remove unneeded words.
- Use minimal punctuation. If there are a lot of commas and semicolons, the sentences are likely too long.
- For long lists, use a bulleted list (instead of paragraph format).
- When using numbers, numerals are easier to read than written words (e.g., 53, instead of fifty-three). Where appropriate, include imperial equivalents in brackets after metric measurements, since many seniors and people from other countries use imperial.

Using the template

There should be a header placed on the first page of the Patient Medication Information with the words in upper case "READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE".

For biosimilars, information should be based on the Canadian Patient Medication Information for the reference biologic drug. Only information that is relevant to indications authorized for the biosimilar should be included. Incorporate changes as necessary where there are differences between the biosimilar and reference biologic drug in, for example, presentation, administration instructions, or allergens in packaging.

At the beginning of the document, the brand name of the drug should appear in upper case, with the proper name of the drug in final dosage form in lower case appearing below the brand name. Where there is no proper name, use the common name in final dosage form. Consider adding, in brackets, a phonetic spelling of the brand name or proper name. If a phonetic spelling of the brand name is included, it should be on the line preceding the brand name. If a phonetic spelling of the proper name is included, it should be on the line following the proper/common name.

The following or similar statement should be included for all drugs:

> *Read this carefully before you start taking [Brand name] and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about [Brand name].*

For biosimilars, include the following statement:

> *[Brand name] is a biosimilar biologic drug (biosimilar) to the reference biologic drug [Reference biologic drug brand name]. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.*

What is [Brand name] used for?

Provide a bullet listing of the authorized indications from Part I. If the product is intended for use as an authorized adjunct to other measures (for example, diagnosis, treatment/therapy), this should be included.

For products that have been authorized under the Notice of Compliance with Conditions (NOC/c) policy, include the following boxed statement:

"For the following indication(s) [Brand name] has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional."

[Provide a bullet listing of the indications from Part I.]

- [text]

[If the Indications section includes lifestyle recommendations as part of the therapy, they should be included here.]

"For the following indication(s) [Brand name] has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada."

[Provide a bullet listing of the indications from Part I.]

- [text]

[If the Indications section includes lifestyle recommendations as part of the therapy, they should be included here.]

The following text must also be included:

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does [Brand name] work?

From 10 CLINICAL PHARMACOLOGY and 14 CLINICAL TRIALS, provide one or two sentences, explaining the mechanism of action of the drug, in plain language, how long it takes to work and how to know if it is working (e.g., improved symptomatology).

For a diagnostic radiopharmaceutical this could include note of approximate imaging times, why more than one imaging session may be required, etc. For a therapeutic radiopharmaceutical, relating the biologic behaviour of the drug- perhaps an affinity for skeletal tissue- with the desired outcome (e.g., palliation of pain) can be helpful. In some instances, attempting to describe the type of radiation and characteristics associated with the particular radioisotope component of the drug may be useful). If use of co-medications are required [e.g., potassium iodide (SSKI)], this can be noted here. For a radiopharmaceutical drug, it is also important to note that the patient will receive a radiation dose.

What are the ingredients in [Brand name]?

Include a complete listing of all medicinal and all non-medicinal ingredients, from 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. Medicinal ingredients should be clearly separated from the non- medicinal ingredients with the headings “Medicinal ingredients” and “Non-medicinal ingredients”.

List medicinal ingredients by their proper names; where there are no proper names, use common names.

List non-medicinal ingredients in alphabetical order, using either proper, common or international nomenclature.

[Brand name] comes in the following dosage forms:

From 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING, provide the available marketed dosage forms and strengths. List the name of the dosage form followed by the strengths in increasing order (e.g., tablet 10 milligrams, 20 milligrams, 100 milligrams).

Do not use [Brand name] if:

For each situation described in 2 CONTRAINDICATIONS, include a corresponding situation in a bulleted list, in plain language, where appropriate.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take [Brand name]. Talk about any health conditions or problems you may have, including if you:

Enter one point for each item listed in 7 WARNINGS AND PRECAUTIONS in a bulleted list, in plain language.

Other warnings you should know about:

This section is included only when there are other general warnings and precautions that are not serious and do not fit under existing headings.

The following or similar statement may be used if there are effects described in Part I that may impair performance of a task requiring attention, including driving and operating machinery:

> *Give yourself time after taking [Brand name] to see how you feel before driving a vehicle or using machinery.*

For radiopharmaceutical drugs, include the following statement(s) as necessary:

> *The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Toilet should be flushed several times after use. If blood or urine gets onto clothing such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.*
>
> *Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.*

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with [Brand name]:

Provide a bulleted list.

Include information to ensure patients are aware of any medications, foods (e.g., citrus, dairy), beverages (e.g., alcohol) or natural health products known to interact with this medication. Serious or significant interactions should be listed in bullet form from the information listed in 9.1 Serious Drug Interactions. If no relevant interactions are known, add a statement to reflect this.

How to take [Brand name]:

Provide information to the patient, or care provider, on how to prepare, reconstitute or administer the drug or operate a device (e.g., metered dose inhaler).

Illustrations that help demonstrate the proper use of a self-administered product (e.g., inhaler, injectable product) are encouraged.

Where appropriate, (e.g., for parenteral products) include directions to examine the solution for product integrity before use, such as:

> *Do not use this medication if it looks cloudy or is leaking.*

Consider the following or similar statement as required:

> *[Brand name] will be given to you by a healthcare professional in a healthcare setting.*

For radiopharmaceuticals, the following or similar statement should be used:

> *[product] will be given to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.*

Usual dose

From the 4 DOSAGE AND ADMINISTRATION section, provide the usual dose, when to take it, how to take it, and other related details.

Overdose

From the 5 OVERDOSAGE section, provide information on what to do if the individual has taken too much medication. This could include overdose with a single dose or a cumulative dosing, accidental consumption by a child, and what measures the patient should take in the event that an overdosage may have occurred.

The following boxed statement is to be added at the end of the narrative section. The statement may be modified to provide the most appropriate advice according to current standards of care for this drug product:

> *If you think you, or a person you are caring for, have taken too much [Brand name], contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.*

Missed dose

From the 4.5 Missed Dose section, provide information on what to do if a dose is missed. The following statements are an examples of what may be used:

> *If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.*
>
> or
>
> *If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.*

For antibiotics:

> *If you missed a dose of this medication, take it as soon as you remember. This will help to keep a constant amount of medication in your blood. But, if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.*

What are possible side effects from using [Brand name]?

This section should include a brief summary of the self-limiting and serious side effects and the action patients should take when experiencing them. The information to be included will be determined in consultation with the sponsor and Health Canada.

The following or similar statement should be included at the beginning of the side effects section:

> *These are not all the possible side effects you may have when taking [Brand Name]. If you have any side effects not listed here, tell your healthcare professional.*

Text

Self-limiting side effects should be described in narrative format. Self-limiting side effects are considered to be those that generally don't require medical attention and will usually go away as the body adjusts to the drug. In cases where this may not be easily understood or predictable, a statement may be added to help the patient understand what course of action they should take. The effects should be grouped by frequency using the terminology provided by the Council for International Organizations of Medical Sciences (CIOMS) (e.g., common, rare). A statement of the risk of dependency, if applicable, should be included here.

Table

All serious side effects should be included in the table. To avoid duplication they do not need to be repeated in the text. Whether the patient can do something about the effect should be used as the criteria for including side effects in the table. The term 'serious side effects' is one that is easily understood by the patient and does not adhere to any international guideline or standard definition of 'serious adverse event. The side effects should be grouped by frequency using the CIOMS terminology. Within each group the effects should be listed alphabetically.

The table should always follow the text.

For serious side effects, instructions to discontinue the use of the product (if safe to do so) should be provided.

Footnotes should not be added to the serious side effects table.

The following or similar statement should be included after the serious side effects table:

> *If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.*

Boxed instructions for reporting side effects called "Reporting Side Effects", and "Reporting Suspected Side Effects for Vaccines" have been included in the master template. Please choose the reporting box that is most appropriate for the product.

Storage

Include a brief description of the storage and disposal instructions as provided in 11 STORAGE, STABILITY AND DISPOSAL.

The following or similar statement should be included for all products:

> *Keep out of reach and sight of children.*

If you want more information about <Brand name>:

For general instructions on the information contained in Patient Medication Information, where to find the full product monograph, how to contact the sponsor, the manufacturer's website and toll free number should be provided. The following or similar statement should be included:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html, the manufacturer's website <www.website.document>; or, by calling 1-800-<telephone number>.

A packaged drug product may remain in the distribution chain for some time after manufacture, depending on the expiry date and turnover at the retail level. Therefore, the revision date on the Patient Medication Information leaflet may not reflect the most recent revision of the information. The sponsor may add a statement similar to the following:

> *This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.*

The only website links that can be listed are those that refer to the product monograph and Patient Medication Information. References or websites containing any information other than what has been authorized by Health Canada are unacceptable.

Date

When any part of the product monograph is revised, the revision date should be reflected as the "Date of Revision" on the title page, and as "Last Revised" date in Patient Medication Information. In the case where revisions are only made to the Patient Medication Information, the title page of the product monograph should also reflect this revision date.

GLOSSARY

Adverse Drug Reaction: a noxious and unintended response to a drug which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function (Ref: C.01.001, *Food and Drug Regulations*).

The International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals For Human Use defines adverse drug reaction in both pre-approval and post-market settings, in the guideline: Clinical Safety Data Management: Definitions and Standards For Expedited Reporting E2A.

- in the pre-approval setting: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions;
- in the post-marketed setting: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

Adverse Event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (Ref: ICH - Clinical Safety Data Management: Definitions and Standards For Expedited Reporting E2A).

Biologic drug: a drug listed in Schedule D to the Food and Drugs Act. Schedule D lists individual products (such as insulin), product classes (such as immunizing agents), references to particular sources (such as "drugs, other than antibiotics, prepared from microorganisms"), and methodology (such as "drugs obtained by recombinant DNA procedures"). Biologic drugs are derived through the metabolic activity of living organisms and tend to be significantly more variable and structurally complex than chemically synthesized drugs. (Ref: Health Canada Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs, April 20, 2017)

Biosimilar biologic drug: a biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. A biosimilar relies in part on prior information regarding safety, efficacy and effectiveness that is deemed relevant due to the demonstration of similarity to the reference biologic drug and which influences the amount and type of original data required. Biosimilar biologic drugs were previously referred to as Subsequent Entry Biologics.

Brand Name: with reference to a drug, the name, whether or not including the name of any manufacturer, corporation, partnership or individual, in English or French,

a) that is assigned to the drug by its manufacturer;
b) under which the drug is sold or advertised; and
c) that is used to distinguish the drug (Ref: C.01.001, *Food and Drug Regulations*).

Canadian Reference Product: a) a drug in respect of which a notice of compliance is issued pursuant to section C.08.004 and which is marketed in Canada by the innovator of the drug,

b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued pursuant to section C.08.004 cannot be used for that purpose because it is no longer marketed in Canada, or

c) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph (a) (Ref: C.08.001.1, *Food and Drug Regulations*).

Clinically Significant Reactions: those reactions that affect prescribing because of their severity and consequent influence on the decision to use the drug, because it is critical for the safe use of the drug to monitor patients for them or because measures can be taken to prevent or mitigate harm. [Ref: United States Food and Drug Administration (FDA)].

Common Adverse Drug Reaction: an adverse drug reaction with a frequency of ≥1/100 and <1/10 (≥1% and <10%). [Ref: Council for International Organizations of Medical Science (CIOMS) convention].

Common Name: with reference to a drug, the name in English or French by which the drug is

a) commonly known; and
b) designated in scientific or technical journals, other than the publications referred to in Schedule B to the Act [e.g., United States Adopted Name (USAN), British Approved Name (BAN), International Nonproprietary Name (INN), etc.] (Ref: C.01.001, *Food and Drug Regulations*).

Crossover Study: different therapies are tested in the same individual; therefore, subjects act as their own control.

Dosage Form: a pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients (Ref: ICH Q1A).

Drug Product: the dosage form in the final immediate packaging intended for marketing (Ref: ICH Q1A).

Drug Substance: the unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form (Ref: ICH Q1A).

Generic Name: see Proper Name.

Genetic Polymorphism: intersubject variability in blood concentration following drug administration observed between individuals of different ethnic groups or within the same homogenous population. For example, individuals who for genetic reasons, are either "fast" or "slow" metabolizers.

Geometric Mean: a measure of central tendency calculated by multiplying a series of numbers and taking the n^{th} root of the product, where n is the number of items in the series. The geometric mean is useful to determine "average factors". It is often used when finding an average for numbers presented as percentages.

Multicentre Study: conducted at different institutions with all the data combined into one study.

New Drug: a) a drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug;

b) a drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug; or

c) a drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug (Ref: C.08.001 *Food and Drug Regulations*).

Notice of Compliance: a notice issued under section C.08.004 of the *Food and Drug Regulations*.

Parallel Study: control subjects are administered a placebo or active standard therapy at the same time as other subjects are administered experimental treatment.

Perioperative: refers to the time before, during or after surgery.

Photoallergic: a delayed immunologic type of photosensitivity involving a chemical substance to which the individual has become previously sensitized and radiant energy (Ref: Dorlands).

Photosensitivity: an abnormal cutaneous response involving the interaction between photosensitizing substances and sunlight or filtered or artificial light at wave lengths of 280-400 nm. There are two main types: photoallergy and phototoxicity.

Phototoxicity: a nonimmune, chemically induced type of photosensitivity.

Pictogram: a picture like symbol used to convey a particular meaning (e.g., a non-smoking symbol).

Professed Standard: products for which no prescribed or compendial standard exists. The term refers to the label claims for quality and potency.

Proper Name: with reference to a drug, the name in English or French:

a) assigned to the drug in section C.01.002,
b) that appears in bold-face type for the drug in these Regulations and, where the drug is dispensed in a form other than that described in this Part the name of the dispensing form,
c) specified in the Canadian licence in the case of drugs included in Schedule C or Schedule D to the Act, or
d) assigned in any of the publications mentioned in Schedule B to the Act in the case of drugs not included in paragraph (a), (b) or (c) (Ref: C.01.001, *Food and Drug Regulations*).

Proprietary Name: see Brand Name.

Rare Adverse Drug Reaction: an adverse drug reaction with a frequency of ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%) (Ref: CIOMS convention).

Reference Biologic Drug: a biologic drug authorized on the basis of a complete quality, non-clinical, and clinical data package, to which a biosimilar is compared to demonstrate similarity.

Route of Administration: indicates the part of the body on which, through which or into which the product is to be introduced (Ref: Pharmeuropa, Standard Terms, January 2000).

Serious Adverse Drug Reaction: means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death (Ref: C.01.001, *Food and Drug Regulations*).

Serious Adverse Event: (experience) or reaction is any untoward medical occurrence that at any dose results in death; is life threatening (Ref: ICH - Clinical Safety Data Management: Definitions and Standards For Expedited Reporting E2A).

Subsequent Entry Product: a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients.

Uncommon Adverse Drug Reaction: an adverse drug reaction with a frequency of ≥1/1,000 and <1/100 (≥0.1% and <1%) (Ref: CIOMS convention).

Very Common Adverse Drug Reaction: an adverse drug reaction with a frequency of ≥1/10 (≥10%) (Ref: CIOMS convention).

Very Rare Adverse Drug Reaction: an adverse drug reaction with a frequency of <1/10,000 (<0.01%) (Ref: CIOMS convention).

---

[1] ATC/DDD Index 2014 (www.whocc.no/atc_ddd_index)
[2] European Commission, A Guideline on Summary of Product Characteristics (SmPC), September 2009, revision 2 https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[3] ICH Topic E 11Clinical Investigation of Medicinal Products in the Paediatric Population, January 2001; ICH Harmonised Guideline, Addendum To ICH E11: Clinical Investigation Of Medicinal Products In The Pediatric Population, E11 (R1), Final version, August 18, 2017
[4] Extent of exposure categories are based on Council for International Organizations of Medical Sciences (CIOMS).
[5] ICH Topic E 11Clinical Investigation of Medicinal Products in the Paediatric Population, January 2001; ICH Harmonised Guideline, Addendum To ICH E11: Clinical Investigation Of Medicinal Products In The Pediatric Population, E11 (R1), Final version, August 18, 2017
[6] C.01.001, Food and Drug Regulations
[7] ICH Guidance On Nonclinical Safety Studies For The Conduct Of Human Clinical Trials And Marketing Authorization For Pharmaceuticals, M3(R2), June 11, 2009
[8] Canadian Public Health Association, 2002