Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments




Product Monograph- Do′s and Don′ts

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Product Monograph

- Part I Health Professional Information
  =prescribing information
  Part II Scientific Information
  - supporting data for Part I

  Part III Consumer Information
  - from Parts I, II, lay language

Part I- Health Professional

- **Summary of Product Information**
- **Indications**
- **Contraindications**
- **Warnings and Precautions**
- **Adverse Reactions, Drug Interactions**
- **Dosage and Administration, Overdosage**
- **Action and Clinical Pharmacology**
- **Storage and Stability, Special Handling**
- **Dosage Forms, Composition and Packaging**

Summary Product Information

- **Do:**
- **Include all dosage forms**
- **Clear declaration strengths as base or salt**
- **Clinically relevant NMIs**
- **X reference to Dosage Forms, Composition and Packaging**

- **Don't: Mix different strengths with different dosage forms**

Indications

- **Do:**
- **Point form listing of Indications per se,**
- **Indication supported by data**
- **Single vs. adjunct therapy, or both**
- **Special restrictions , in prescriber, specialist use**

- **Don’t mix indications with supporting text**
- **Don’t expand indications beyond data**
- **Don’t use ambiguous language**
- **Don’t include general disease information**

Indications- Patient Subsets

- Do:
- Indicate relevant use, or not in subset
- If no data, indicate
- Cross-reference to other sections
- Point form

- Don’t: mix patient subset pharmacokinetic, adverse reactions, warnings in this section, leave to cross-referenced section

  (Keep it simple)

Contraindications

- Do:
- Indicate clearly do not use (any circumstance)
- Contraindicated drug interactions cross-referenced
- Point form

- Don’t qualify to allow possible use
- Don’t mix warnings with contraindications
- Don’t use extraneous text

  (related information can go in warnings)

Serious Warnings Box

- Do:
- Point form, <20 lines
- From any part of PM
- Only significant/ life threatening
- May include drug interaction
- Cross-reference
- Restrictions in use

- Don’t repeat contraindications
- Don’t add unnecessary text

  (Other text X-ref. to other section)
- Don’t add useless cross-references

Warnings and Precautions

- **Do:**
- **Organ system sub-headings**
- **Alphabetical**
- **General: info. does not fit elsewhere**
- **Further sub-headers:**

Immune: Infection

Hypersensitivity

- **Don't mix animal data with human data**

(Most animal data in other sections)

Warnings- Carcinogenesis , Mutagenesis

- Do:
- Concise warning
- Human data, if any
- Summary and X-ref to Toxicology
- If only animal data, use limited amount and X-ref. to Toxicology

- Don’t add extraneous information which belongs Toxicology

Warnings- Dependence, Tolerance

- Do indicate:
- Abuse potential
- Physical, psychological
- Amount, time to dependence
- Characteristics dep.
- Withdrawal charact.
- Treatment

Warnings- Endocrine, Metabolism

- **Do indicate:**
- **Genetic polymorphism- population, if any**
- **Slow, fast metabolizers, if clinically relevant**
- **Cytochrome P450 (x-ref. to Interactions)**
- **Diabetes**

Warnings- Immune

- Do indicate:
- Altered-activation or suppression
- Characteristics of alteration
- X-reference to Side Effects, if applicable
- Infection
- Hypersensitivity

Warnings- Peri-operative

- Do indicate:
- Drug management, before, after, during
- Discontinuation
- Dosage↑↓

Special Populations-Pregnant

- Do:
- Specify exact warning
- Specify human/ animal data
- Systemic absorption
- Teratogenic risk
- Exposure-clinical trials

- Don't include more than minimal animal data

  [X-reference to animal data]

Special Populations- Nursing

- Do indicate:
- Excretion- human breast milk
- If not, animal data?
- Expected (potential) ADR in infants
- General recommendation
- Alternatives

- Don’t use ambiguous language

Special Populations- Pediatrics

- **Do:**
- **Specify age (correspond clinical)**
- **Special hazards, monitoring**
- **Differences in response ,**
- **X-ref to other sections, if further**
- **If no data, indicate such**

- **Don't include pharmacokinetic, ADR….**

Special Populations-Geriatrics

- Do:
- Specify age (65, 75)
- Special hazards, monitoring
- X-Ref. to hepatic, renal, if required
- If special ADR, X-Ref. to ADR
- If no data, indicate

- Don’t include pharmacokinetic, ADR, other information

Adverse Reactions

- Do:
- Separate clinical trial vs. post-market
- MedDRa terms
- CIOMS frequency terms
- Isolated reports
- Table

- Don’t mix Adverse Events and Adverse Drug Reactions
- If data is old, may be no clinical trial ADR, just ADR

ADR- Overview

- Do indicate:
- Serious ADR's
- Factors affecting serious ADR's
- ADR's requiring medical intervention
- Most frequent ADRs
- Meant as a concise summary

- Don't add extraneous text, (put text in other sections)
- Don't add safety information as disguised/ implied off-label use (ie. pediatric….)

Clinical Trials ADRs 1 of 4

- **Do:**
- **General statement**
- **Data source- study design, control, exposure, exclusions**
- **Table common, very common**
- **Many tables –different populations, indications, formulations**

- **Don't use massive, undifferentiated text**

Clinical Trials ADRs- 2 of 4

- **Do:**
- **Table: body system**
- **By ↓ frequency**
- Denominator (n), %
- Pooled data, if justified
- Dose-response (rare)
- Plus narrative, if needed

- **Don't use massive undifferentiated text**
- **SNDS- Don't submit core safety data updates to hide or disguise new, unsupported information**

Clinical Trials ADRs 3 of 4 Less Common ADRs

- Do:
- < 1%
- Listing by body system
- Alphabetical
- Narrative

Clinical trials 4 of 4- Hematological, Clinical Chemistry

- **Do: Ideally**
- **Table 1- Hematologic**
- **Table 2- Clinical**
- **Number patients**
- **Define normal values**
- **Range values**
- **Significant difference** ?

- **Don't forget to indicate whether changes are considered clinically significant**
- **Don't include pages of tables with meaningless data. Convert to narrative**

Post- market ADRs

- **Do:**
- **Serious, unexpected**
- **Canadian, international**
- **Post- market surveillance/ Phase IV clinical trials**
- **Narrative or table if much information**

- **Don't present an undifferentiated block of text**

Drug Interactions
Serious Drug Interactions Box

- **Do:**
- **<u>Only</u> serious, life-threatening**
- **Brief bullets, <20 lines**
- **X-ref. to DI text if further information**
- **If drug interactions in Contraindications, must be here too**

- **Don't include a box if drug interactions are not serious**

Drug Interactions- Overview

- **Do:**
- **Clinically relevant**
- **Potential, suspected based on CYTP450, QT prolongation, genetic polymorphism**
- **Brief statement(s)**
- **Drug class statements, if any**

- **Don't include clinically insignificant information**

Drug/ Drug Interactions

- **Do:**
- **Clinically relevant**
- **Table, Headings:**
- **a) Common name**
- **b) Level evidence**
- **c) Effect, d) Clinical comment**
- **Studies or potential**
- **If no interaction- indicate**

- **Don't include pharmacokinetic studies (for Part II).**
- **Don't forget to state: <u>No drug interaction studies done</u>, if no drug interactions are noted and if this is the case**

Drug- Food Interactions
Drug- Herb Interactions

- **Do:**
- **Known, or potential**
  (i.e. grapefruit juice
  St. John's Wort)
- **Practical advice**
  (i.e. X-ref. to Dosage)
- **Table, if needed**
- **If no interactions, indicate**

Drug-Laboratory Test Interaction

- Do:
- Lab tests altered by drug
- Practical advice

  (i.e. timing)
- Table, if needed
- If no data, indicate

Dosage & Administration Dosing Considerations

- **Do:**
- **Overview safety issues (i.e. age, renal, hepatic, titration, other therapy)**
- **Non-equivalent dosage forms, provide conversion factors**
- **X-ref. to other sections if needed**
- **Brief, point form**

- **Don't add extraneous text belonging in other sections**

Recommended Dosage 1 of 2

- **Do:**
- **Initial dose, titration**
- **Dosage range, maximum daily**
- **Maintenance, duration**
- **Details discontinuation**
- **Dosage each indication**

- **Don’t mix different dosages for different indications, conditions, adjustments**

Recommended Dosage 2 of 2

- **Do: Dosage adjustments:**
- **Special populations**
- **Special pathologies: (renal, hepatic…)**
- **Timing (day, night)**
- **Conditions (food, no food)**

- **Don't include warnings, special handling, pharmacokinetics…**

Administration 1 of 2

- **Do: Methods**
- **Do not chew (enteric**
- **Unusual forms: inhalers, implants…**
- **Drug combination delivery**
- **Oral- reconstitution**

Administration 2 of 2- Parenteral

- **Do:**
- **Reconstitution table: diluent, volumes, concentration…**
- **Further infusion**
- **Compatible infusion fluids**
- **Storage undiluted, diluted**
- **Preparation precautions**

Overdosage

- **Do:**
- **Signs, symptoms, if any**
- **Current management**
- **Human lethal dose, if available**
- **Maximum dose with recovery**
- **Hazardous, ineffective treatment procedures**

- **Don’t forget to update regularly**

Action and Clinical Pharmacology

- **Do:**
- **Concise synopsis**
- **Mechanism action**
- **Pharmacodynamics (dose response, safety, effectiveness)**
- **Human relevance**
- **Pharmacokinetics**

- **Don’t include detailed information from Detailed Pharmacology**

Pharmacokinetics

- **Do:**
- **Summary table**
- **Absorption characteristics (AUC, Tmax, onset, food..)**
- **Distribution characteristics**

  (protein binding, sites, extent..)
- **Metabolism (sites, pathways, CYTP450, first pass, dose dependent)**
- **Excretion (route, half-life, linearity, non-linearity, …)**

Pharmacokinetics- Special Populations, Conditions

- **Do, ideally:**
- **Pediatrics, geriatrics**
- **Gender, race**
- **Genetic polymorphism**
- **Renal, hepatic insufficiency or other condition**

- **Don't include pharmacokinetic drug-drug (Part II)**
- **Don't include animal, in vitro pharmacokinetic (Part II)**

Storage and Stability

- **Do:**
- **Studies support stability**
- **Temperature, light, humidity, other**
- **Reconstituted-Storage period, conditions, duration**
- **Incompatabilities (drugs, diluents, infusion, containers….)**

- **Don’t mix different storage directions with different dosage forms**

Special Handling Instructions

- **Do:**
- **For potentially hazardous (cytotoxic**
- **, mutagenic)**
- **Special (i.e. fume hood, gloves, clothing, breathing)**
- **Decontamination**
- **Safe disposal**

- **Don't forget to X-reference to other sections (Warnings, Administration) if necessary**

Dosage Forms, Composition and Packaging

- **DO:**
- **All dosage forms, strengths**
- **All nonmedicinals by common/proper name**
- **All packaging formats and sizes**
- **Packaging inf. related to safety (i.e. latex)**

- **Don't use brand names for NMI's**
- **Don't forget quantitation for medicinal ingredients**

Part II- Sections

- Pharmaceutical Information
- Clinical Trials
- Detailed Pharmacology
- Microbiology
- Toxicology
- References

Part II- Pharmaceutical Information

- Do:
- Proper name, common name
- Chemical name
- Molecular formula and mass
- Structural formula
- Physiochemical
- Reviewed by BPS

- Don’t:
- Don’t forget diagram for structural formula

Part II- Clinical Trials 1 of 4

- **Do:**
- **Demographics, numbers**
- **Age, gender, race**
- **Trial design**
- **Dose, route,duration**
- **Results (1˚, 2˚)**
- **Placebo, active control**

- Don’t forget annotation, tabular results, comparative bioavailability, different tables for different dosage forms
- If no clinical data, indicate such

Clinical trials- 2 of 4 Demographics

- **Age, gender, race**
- **Other (renal, hepatic**
- **Genetic polymorphism**
- **All subjects accounted for**
- **Sample size**
- **Table**

Clinical trials 3 of 4
Study design

- **Describe: parallel, cross-over, multi- ctr**
- **Adequate, well-controlled**
- **Supports safety, efficacy**
- **Recognized controls**
- **Dose, range, duration**
- **Table**

- **Don't do comparative efficacy/ safety unless required**
- **Don't submit studies implying unapproved indications**
- **PM conversions-Don't include old comparative claims that are not supported**

Clinical Trials 4 of 4 Results

- **Primary, secondary endpoints for safety, efficacy**
- **Compare treatments vs control (or active comparator)**
- **Results show difference (P value)**
- **Clinically significant**
- **Table**

- PM conversions: If data old, limited, few study reports…etc, better to convert to generic statements

Pivotal Comparative Bioavailability

- **New dosage forms where S/E depends on comp. bioavailability**
- **Study design- single, multiple dose**
- **Fasting-fed, cross-over, parallel….**
- **Number, male- female**
- **Tabular results with preceding narrative**
- **Don’t forget to include identities of compared products.**

Detailed Pharmacology 1 of 3

- **Human, animal**
- **In-vivo, in-vitro**
- **Meaningful detail**
- **Animal only if human data lacking**
- **Pharmacodynamics, Pharmacokinetics**
- **Absorption**
- **Avoid narrative and use tables if possible**
- **Avoid speculation, extrapolation of pharmaco(dynamic) (kinetic) data to clinical use**

Detailed Pharmacology 2 of 3

- **Bioavailability**
- **Blood, tissue level**
- **Distribution, binding**
- **Metabolism, metabolites, rate**
- **Enzyme induction, inhibition, saturation**
- **Excretion, route, manner**

- **Don’t put clinical efficacy studies here**

Clinical Pharmacology 3 of 3 Influencing Factors

- **Age, gender, pregnancy**
- **Genetic (if any data)**
- **Disease, condition**
- **pH GI tract**
- **Drug interactions**
- **Pharmacokinetic factors affect activity, toxicity, disease, physiology….**

- **Don't forget to cross-reference to other sections**
- **Avoid narrative, use tables.**

Microbiology

- **<u>All</u> microbiology drugs**
- **Summary laboratory studies**
- **Divide into in- vivo and in-vitro studies**
- **Susceptability testing**
- **Reference pathogens**
- **Table presentations preferred**

- **[Microbiology section deleted for most drugs]**

Toxicology 1 of 2

- **Do:**
- **Human tolerance studies (if any)**
- **Animal, human**
- **Animal: description, species, route, dosage, results, abnormal results**
- **Single, multiple dose**
- **Short –term, long-term**

- **Don't:**
- **Avoid undifferentiated text, use tables**
- **Don't combine animal, human data**

Toxicology 2 of 2

- **Reproductive**
- **Special studies (i.e. ophthamologic)**
- **Carcinogenic-animal studies, human potential**
- **Mutagenesis**
- **If mutagenic, cross-ref. to Warnings**

References

- **Do:**
- **Support pivotal clinical studies, other studies in CT**
- **Support pre-clinical**
- **Authoritative papers on use of drug**
- **Numbered to X-ref.**
- **Published, unpublished**

- **Generics: Don't forget to include reference to latest applicable innovator PM.**

Consumer Information- Sections

- **What the medication is used for?**
- **What it does?**
- **When should it not be used?**
- **What are the medicinal, non-medicinal ingredients?**
- **Dosage Forms**
- **Warnings and Precautions**
- **Interactions, Proper Use, Side Effects**
- **Storage, Reporting Side Effects, More Information, Latest date of revision**

Part III- Consumer Information

- **Do:**
- **Part of all PM's in new format including hospital, clinic….**
- **Reflects Parts I, II**
- **Simple, clear, lay language, bullets**
- **Separate CI for major differences in use (migraine,hypertension)**
- **Don't write as promotional**
- **Avoid vague, ambiguous, scientific language, language above Grade 8 level.**
- **Avoid text > 2,3 pages**
- **Don't use pictograms**

Part III- Template

- **Do:**
- **Use template**
- **2 column format**
- **Standard headings**
- **Bullets, point form**
- **Standard disclaimers**
- **Easy to read, retrieve information**

- **Avoid repetition except when necessary, i.e. severe allergic reaction (may be in "When it should not be used", Warnings, Side Effects)**

What the medication is used for?

- **From Indications**
- **Single use, adjunctive use (HIV medication used with other HIV medications)**
- **First line, 2nd line**
- **Lifestyle (i.e. diet with anti-diabetic drugs, if part of therapy)**
- **Point form**

- **Don't add mechanism of action (What it does)**
- **Don't add directions for use or other information belonging in other sections**

What the medication does?

- **From Action and Clinical Pharmacol.**
- **Mechanism action, briefly (1-2 sentences)**
- **Onset action (When? How?....)**
- **Improved symptoms**
- **Lay language**

- **Avoid over-explanation**
- **Avoid complex terminology**

When the medication should not be used

- **Reflects all Contraindications**
- **Point form**
- **Lay language if possible (or terminology plus explanation)**
- **Cross-ref. to Warnings any related information(i.e. hepatotoxicity)**
- **Avoid ambiguity (Use clear language: Do not use….)**
- **Don't mix warnings in text**
- **Don't turn a Contraindication into a Warning by use of language(i.e.- Do not use… revised: Not recommended…)**

Product Identity

- **Medicinal ingredient by proper or common name**
- **Dosage form**
- **Entire salt, if applicable**
- **If quantity shown, specify base or salt**
- **If quantified as base, also ensure full salt is mentioned**
- **Don’t mix up quantity in terms of base or salt**

Serious Warnings and Precautions Box

- **Only if in Part I**
- **Beginning section**
- **Lay language, or if not possible, some explanation**
- **Cross-reference to Warnings if needed**
- **Point form, concise**
- **Avoid long text (X-ref. to Warnings)**
- **Don’t add lesser Warnings**
- **Don’t add directions or other information from other sections**

Part III- Warnings and Precautions

- **From Parts I, II**
- **Talk to doctor before: (current/past conditions,diseases, medication, medical procedures,….**
- **Medication effects**
- **Developments during treatment**
- **Contact your doctor if**
- **Avoid massive text (use many headings)**
- **Avoid adding side effects here, unless necessary to indicate or support a warning**

Interactions with Medication

- **Talk to your doctor if using medications…**
- **All Serious Drug Interactions, Part1,**
- **Contraindications**
- **All needing dosage ↓↑**
- **Don't change dosage other drugs unless….**
- **Drug-food, Drug-herb**
- **X-ref other sections (Warnings, Directions…**
- **Don't mention drugs having no significant effect (no negative list)**
- **If drugs no longer marketed in Canada, don't forget to mention this fact as note or footnote**

Proper Use of Medication 1 of 3

- **Usual dose and/or as prescribed by….**
- **Separate adult, pediatric dose**
- **Separate dose per indication if different**
- **Initial, loading, maintenance dose**
- **Single / daily, maximum daily**
- **Timing (day, night…)**

- **Don’t mix different dosages with different conditions, populations, ages (separate)**
- **Don’t mix warnings in directions**

Proper Use of Medication 2 of 3

- **Onset of action (when starts to work)**
- **With food or not**
- **Concomitant meds**
- **Incompatabilities (ie antacids, timing)**
- **Dosage tables (i.e. pediatric by weight)**
- **Special administration**
- **(inhalers, patches….)**

- **Don't forget to cross-reference to other sections if necessary (Interactions, Warnings, Side Effects…)**

Proper Use of Medication 3 of 3

- **Special handling directions (toxic drugs, avoid inhaling, eye contact)**
- **Special disposal directions (return to pharmacist, patches)**
- **Missed dose,**
- **Overdose**

Side Effects- Less Serious

- **Narrative- self-limiting, goes away**
- **No medical attention**
- **Grouped by frequency (CIOMS)**
- **Risk dependency if any**
- **Statement (if applicable) : If X persists, or becomes bothersome, contact your doctor.**

- **Don't forget to include all significant and common (i.e. > 4%) or very common side effects, that could be expected.**

Side Effects- Serious

- **Tabular: Side effect plus symptoms: (i.e. Liver problems: abdominal pain, nausea, jaundice…etc..)**
- **Frequency (or Isolated reports)**
- **What to Do**
- **Narrative, if needed, precedes table**

- **Don't put less serious side effects in table**
- **Don't forget standard closing statement (This is not a complete list…..)**

Reporting Side Effects/ More Information/ Date

- **Follow ADR reporting template**
- **Provide directions to obtain complete PM and to contact sponsor**
- **Provide last revised date for Part III**
- **[Optional: For those without internet access, please provide a phone number, and for those without a phone, also supply a complete mailing address so consumers can contact the manufacturer.]**