Policy document: MEB commentary on the Guideline on Summary of Product Characteristics
September 2009

MEB-27

31 August 2015
# TABLE OF CONTENTS

1. INTRODUCTION ........................................................................................................... 3  
   1.2 Other documents relevant to the SmPC ................................................................. 3  
   1.3 Combined SmPC ................................................................................................... 3  

2. COMMENTARY PER SECTION OF THE QRD TEMPLATE .................................. 4  
   1 – NAME OF THE MEDICINAL PRODUCT ............................................................... 4  
   2 – QUALITATIVE AND QUANTITATIVE COMPOSITION ..................................... 4  
   3 – PHARMACEUTICAL FORM ................................................................................. 4  
   4 – CLINICAL PARTICULARS ..................................................................................... 5  
      4.1 – Therapeutic indications .................................................................................. 5  
      4.2 – Posology and method of administration ........................................................ 5  
      4.3 - Contraindications .......................................................................................... 5  
      4.4 – Special warnings and precautions for use ..................................................... 6  
      4.5 - Interactions with other medicinal products and other forms of interaction .... 6  
      4.6 – Fertility, pregnancy and lactation ................................................................. 6  
      4.7 - Effects on ability to drive and use machines .................................................. 6  
      4.8 – Undesirable effects ....................................................................................... 7  
      4.9 – Overdose ....................................................................................................... 7  
      5 – PHARMACOLOGICAL PROPERTIES ............................................................... 7  
      5.1 – Pharmacodynamic properties ....................................................................... 7  
      5.2 – Pharmacokinetic properties ......................................................................... 8  
      5.3 - Preclinical safety data ................................................................................... 8  
      6 – PHARMACEUTICAL PARTICULARS .................................................................. 8  
      6.1 List of excipients ............................................................................................... 8  
      6.2 Incompatibilities ............................................................................................. 8  
      6.3 Shelf life ........................................................................................................... 8  
      6.4 Special precautions for storage ....................................................................... 8  
      6.5 Nature and contents of container ..................................................................... 8  
      6.6 Special precautions for disposal <and other handling> ..................................... 9  

7 - MARKETING AUTHORISATION HOLDER ......................................................... 9  

8 – MARKETING AUTHORISATION NUMBER(S) ..................................................... 9  

9 – DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION ....... 9  

10 – DATE OF REVISION OF THE TEXT ................................................................. 10  

<11 – DOSIMETRY> ..................................................................................................... 10  

<12 – INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS> ......... 10
1. Introduction

This document replaces ‘MEB commentary on the Guideline on Summary of Product Characteristics October 2005’.

The second revision of the ‘Guideline on Summary of Product Characteristics (SmPC)’ was published in September 2009. The most important area for attention in Revision 2 is the implementation of requirements outlined in the paediatric regulation (EC 1901/2006) regarding the distinction of different age categories in various relevant categories.

Information already included in the Guideline and/or the QRD template is not repeated in this policy document. This document only serves as a commentary on the Guideline.

1.2 Other documents relevant to the SmPC

Via European Committee (Eudralex)

Via EMA
- Annotated QRD template for Centralised procedures: See ‘Product information’ – ‘Product information templates’ Quality Review of Documents human product-information annotated template (English)
- Guideline on the excipients in the label and the package leaflet of medicinal products for human use

Via MEB
- MEB-08 Guideline on the excipients in the label and the package leaflet of medicinal products for human use (Dutch translation)
- MEB-13 Nomenclature pharmaceutical products
- Message on MEB website “What are the consequences for the product information of generic products in relation to usage patents?”
- Policy document “MEB policy on marketing authorisations without Dutch translations of the product information and/or mock-ups”.

1.3 Combined SmPC

- If the SmPC for all RVG numbers contains the same information (for example in case there are multiple dosages for one product), the MEB feels it useful to combine the SmPC so that it is immediately clear other doses are also available.

- If the SmPC for the individual RVG numbers contains different information, the following applies: During MRP/DCP, it may be desirable to work with a combined text, in which information specific to (a) certain dose(s) can be highlighted in grey. This is a working document. Such a combined text can also be used during national implementation. However, the texts must be split upon
completion of the national implementation, as it is not considered desirable for a final, national version to contain highlighted text. The information specific to certain dosage(s) may be mentioned in writing, however, for example: "The following information applies solely to <product name> x mg".

- The MEB prefers that separate SmPCs are drafted for different pharmaceutical forms. Combining multiple pharmaceutical forms in a single text, as is permitted according to current policy, may be confusing. For existing products, this may have the following practical consequences: if the SmPC is a combined text, for example for three tablets, two suppositories and one fluid for injection, the SmPC is split into three texts: one for the three tablets with different dosages, one for the two suppositories with different dosages and one for the fluid for injection. The SmPCs will be assessed on a case-by-case basis to determine whether they need to be split.

- The original text must be kept intact wherever possible when splitting the documents. This is particularly true for the dosage prescription, even if this cannot be implemented using one dosage or pharmaceutical form, for example if another pharmaceutical form or dosage is required for initiation or cessation of therapy or the treatment of a specific group or a specific indication. See also Chapter 2, section 4.2.

2. Commentary per section of the QRD template

1 – NAME OF THE MEDICINAL PRODUCT

See also the Policy Document "Nomenclature pharmaceutical products" (MEB 13).

If there is no standard term for the pharmaceutical form, a new term may be requested from the European Department for the Quality of Medicines (EDQM). Prior consultation with the MEB is desired.

2 – QUALITATIVE AND QUANTITATIVE COMPOSITION

Where possible, decimals should be avoided when mentioning doses.

For certain excipients, information does not need to be included in section 2, but does need to be included in section 4.4, for example if a product contains less than 1 mmol of sodium per dose. In this case, the amount of sodium does not need to be listed in section 2, and the following statement in section 4.4 will suffice:

This medicinal product contains less than 1 mmol of sodium (23 mg) per <dose>, i.e. is essentially 'sodium-free'.

However, if the product contains more than 1 mmol of sodium per dose, the amount of sodium must be mentioned in section 2, and the following statement should be included in section 4.4:

This medicinal product contains x mmol (or y mg) of sodium per <dose>. Care is required in patients with a sodium-restricted diet.

See the "Guideline on the excipients in the label and the package leaflet of medicinal products for human use".

3 – PHARMACEUTICAL FORM

This section does not require further commentary
4 – CLINICAL PARTICULARS

4.1 – Therapeutic indications

This section does not require further commentary

4.2 – Posology and method of administration

Use instructions for the doctor or other care professionals are placed in this section. Detailed use instructions (such as illustrations) for products to be administered by the patient himself may be included in the package leaflet.

If it has been demonstrated that taking food has no effect on the efficacy of the product, the following standard statement may be included:

"The efficacy of [Product name] is not affected by using food. [Product name] may be used before, during or after the meal".

There may not be any information available for older products in particular. Unless otherwise demonstrated, the following statement should be included:

"It is unknown whether the efficacy of [Product name] is affected by using food. [Product name] should be taken before a meal".

If the SmPC lists dosages that are not achievable using the product in question, this should be mentioned in both the SmPC and the package leaflet.

For simvastatin, for example, the dose varies from 5 to 80 mg. The SmPC for simvastatin 80 may include the following statement:

"The recommended doses are not all possible using this product, however there are products with dosage lower than 80 mg available".

If a patient must use very many tablets, capsules, etc. of a product to achieve the recommended dose, while a similar product is available with a higher dose, this may be mentioned in the SmPC and the package leaflet. For enalapril maleate, for example, the dose varies from 2.5 to 40 mg per day. The SmPC for Enalapril maleate 2.5 may include the following statement:

"The recommended doses are possible with this product. However, there are also products available with a higher dose than 2.5 mg, so fewer tablets will be required per time".

Preparation for Administration (VTGM) of medicinal products for intravenous (IV) and subcutaneous (SC) administration in the home situation

Instructions must be included in the package leaflet for medicinal products that are prepared for administration and administered in the home situation. The SmPC should mention that the product can be prepared and administered in the home situation. The inclusion of self-administration in the home situation in the approved product information indicates that the MEB has determined a positive benefit/risk balance. Only then does it form part of the approved medicinal product and has it been approved by the MEB.

4.3 - Contraindications

This section must only contain all circumstances and patient groups in whom use of the product is absolutely not safe ('absolute' contraindication).

Mention of 'Pregnancy' as a contraindication should only occur under very specific circumstances, namely in case of demonstrable human risk. This means an 'absolute' contraindication, which makes use of the product during pregnancy irresponsible due to expected harmful effects for the foetus. A contraindication based solely on the fact that evidence from animal studies is lacking is not permitted, as this is confusing.
If the simultaneous use with a certain group of medicinal products is contra-indicated, inclusion of only the group or class of medicinal products in this section, with a reference to section 4.5, is sufficient. The list of all the active substances that fall within the contra-indicated group/class can be provided in section 4.5. However, section 4.5 should clearly state that this refers to contra-indicated simultaneous use, with a reference to section 4.3.

4.4 – Special warnings and precautions for use

If serious adverse effects have been reported for a medicinal product when used for an unauthorised indication (so-called off-label use), the following statement should be included in section 4.4:

*Cases of ... (several adverse events) have been reported following use of X for the unauthorized indication...*

The MEB has already decided to include this standard phrase in the SmPC in the above-mentioned situation. This has not yet been defined at the European level.

The inclusion of a "doping warning" will not be permitted in the national product information. As this is legally required in a number of countries, this will have to be marked as a Blue Box in European procedures. Consequently, the following statements or variations thereof will not be approved for the Dutch SmPC or package leaflet:

- <X> is on the doping list
- The use of <X> can result in a positive result in a doping test.
- The use of <X> as a doping agent can pose a health risk.
- In laboratory tests for <xxx>, <X> can result in a false-positive result for doping tests

4.5 - Interactions with other medicinal products and other forms of interaction

In the event of interactions with food, a cross-reference to section 4.2 and 5.2 should be included.

If a European SmPC lists interactions with substances not authorised in The Netherlands, one substance may not simply be replaced by another, even if the substances fall within the same group. This is due to the fact that the interaction may differ per substance.

For example, if the European determined text lists an interaction with warfarin, this cannot automatically be replaced with the coumarin authorised for use in The Netherlands in the Dutch text. This is because interactions are not the same for coumarin and warfarin.

4.6 – Fertility, pregnancy and lactation

Information on the degree of excretion on the active substance and its metabolites in breast milk must always be given. A recommendation regarding whether or not breast-feeding may be continued, only needs to be interrupted temporarily (by pumping and disposing of the milk) or needs to be stopped must be included. Data may not be available for older products in particular. This must be stated as such. Even if no information is available on fertility, "fertility" must be included in the title.

4.7 - Effects on ability to drive and use machines

If an effect is unlikely, the following statement may be included:

"<x> has no or negligible influence on the ability to drive and use machines."
4.8 – Undesirable effects

Only undesirable effects for which a casual association with the product is plausible should be included. All sources of information should be weighed together in this determination. The spontaneous report system assumes that a doctor/pharmacist reports a suspected undesirable effect, because he/she believes there is a causal relationship between use of the substance and the undesirable effect (unless the reporting party explicitly states there is no causal association).

The following Dutch terms have been defined for determination of frequency (frequency according to MedDRA):

- Very common: Zeer vaak
- Common: Vaak
- Uncommon: Soms
- Rare: Zelden
- Very rare: Zeer zelden
- Not known: frequency cannot be estimated: Onbekend: op basis van de bekende gegevens kan de frequentie niet worden vastgesteld

Sub-category paediatric population

Information on undesirable effects observed specifically in children, or the occurrence of undesirable effects in different frequencies in children compared with other populations should be mentioned here.

If possible, this information on undesirable effects and frequency of occurrence should be presented per specific age categories (according to ICH E11 classification).

ICH E11 is not available in Dutch. The MEB proposes the following translations:

- Preterm newborn infants: Premature neonaten
- Term newborn infants: A terme neonaten (0-27 days)
- Infants and toddlers: Zuigelingen en kinderen tot 2 jaar (28 days to 23 months)
- Children: Kinderen (2 to 11 years)
- Adolescents: Jongeren (12 to 16-18 years (depending on region))

4.9 – Overdose

This pertains to ‘acute’ overdose. Chronic overdose and its effects should be listed under section 4.4, insofar as relevant. If an accidental overdose (e.g. oral intake of topical dosage forms by children) can lead to problems, the information about this should be included in this section.

A European defined SmPC may occasionally state that contact should be sought with a specific treatment centre (e.g. the closest toxicological centre). In the translation to the national SmPC, one can refer to the National Toxicology Information Centre (Nationaal Vergiftigingen Informatie Centrum [NVIC]).

5 – PHARMACOLOGICAL PROPERTIES

5.1 – Pharmacodynamic properties

This section does not require further commentary.
5.2 – Pharmacokinetic properties

This section does not require further commentary.

5.3 - Preclinical safety data

This section does not require further commentary.

6 – PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The MEB preference is to list all E numbers, so not only E numbers for excipients listed in the Excipients Guideline.

The Chemical-Pharmaceutical Evaluation Unit (CFB) of the MEB uses the following standard phrase for SmPC evaluations during a European procedure:

In accordance with the Note for Guidance on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use, the addition of E numbers for excipients is only required for those excipients that have to be included on the label.

However, the MEB is of the opinion that the inclusion of E numbers for other excipients may constitute valuable information to patients. Therefore, the MEB requests the following E numbers to be included on a voluntary basis:

6.2 Incompatibilities

This section does not require further commentary.

6.3 Shelf life

This section does not require further commentary.

6.4 Special precautions for storage

This section does not require further commentary.

6.5 Nature and contents of container

All authorised package sizes must be included, including bulk packaging that is not solid directly to patients by packaged by the pharmacy. An outer box with smaller packs (multi-unit packs for distribution) does not need to be mentioned, however, so: a pot with 500 tablets should be mentioned, but an outer box with 10 packs of 50 tablets should not.

Particularly in mutual recognition procedures, but also in national procedures, not all packages submitted are actually marketed in The Netherlands. In this case, the standard phrase "Not all pack sizes may be marketed" should be included. This does not require further specification.

The EAV packs are not listed in the SmPC guideline. However, if the EAV pack contains the same packing materials/is the same size as already authorized packs listed in the EU SmPC, this may be mentioned in the national SmPC. An EAV pack may only be added to the SmPC during the national implementation of a marketing authorisation application or a variation involving the SmPC; but only as long as the materials/size are consistent with the strip packaging listed in the SmPC. Additions to the
package leaflet/pack texts are possible without a MRP variation and via a national article 61(3) procedure.

It is possible that the SmPC established at a European level states that a blister holder has been added to the packaging. This can be indicated using the sample sentence: “The packaging contains blisters and a blister holder”. As is the case with the packaging sizes, the package leaflet should state: “The blister holder is not marketed in all countries.”.

The European SmPC can also include the term “childproof” or “senior-citizen friendly”. Both terms are not acceptable in the Dutch SmPC. The term “senior-citizen” is subjective and does not provide a proper description of the target group. The MEB is of the opinion that there is no such thing as an entirely childproof package, but only of a deterrent package. The Board therefore considers claims concerning child safety as misleading. Therefore, the Board will not accept claims concerning child safety on the packaging. If an application is made during an MRP/DCP procedure concerning a claim about child safety on the packaging, this will fall under the “blue box concept” during the procedure and this claim will not be accepted on the Dutch packaging.

For example, the claim “Difficult for children to open” is not permitted.

### 6.6 Special precautions for disposal <and other handling>

Information regarding preparation of the product for administration (for example dissolving a powder for injection) is placed in this section, regardless of who prepares the product. General information about administration (also if the product is administered by a doctor or other care professional) is included in section 4.2. The information in section 4.2 must be brief; the patient leaflet is the correct place for providing extensive instructions.

This section can also include information about compatibility with other products or solutions, which are included in the authorisation dossier. If the marketing authorisation holder wishes to include information about compatibility, all available data must be included in the authorisation dossier. It is not permitted to refer to the marketing authorisation holder for more information.

### 7 - MARKETING AUTHORISATION HOLDER

This section does not require further commentary.

### 8 – MARKETING AUTHORISATION NUMBER(S)

This section does not require further commentary.

### 9 – DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Upon first renewal, the renewal date as agreed upon at the European level is listed in section 9, under marketing authorisation date. Upon the next renewal (either a renewal for an indeterminate period or another renewal for 5 years), the previous renewal date is replaced by the new renewal date. This section is completed by the MEB.
10 – DATE OF REVISION OF THE TEXT

Depending on the preceding procedure (variation, renewal, withdrawal of 1 dose, etc.), the MEB will determine which date will be filled out. This section is left blank for new marketing authorisations.

<11 – DOSIMETRY>

This section does not require further commentary.

<12 – INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS>

This section does not require further commentary.