CBG MEB

MEDICINES EVALUATION BOARD

Policy document MEB 27

MEB commentary on the Guideline on Summary of Product Characteristics

September 2017

1. Contents

2. Abbreviations and definitions

GS	General Sales
CMDh	Coordination group for Mutual recognition and Decentralised procedures human *The European committee for mutual recognition and decentralised procedures*
CMS	Concerned Member State *An EU member state that is not responsible for the assessment of a particular product*
CBG	College ter Beoordeling van Geneesmiddelen *Medicines Evaluation Board*
DCP	Decentralised Procedure
EAG	Unit Dispensing Suitable Packaging
EAV	Unit Dispensing Packaging
EMA	European Medicines Agency
EU	European Union
IGJ	Health and Youth Care Inspectorate
MEB	Medicines Evaluation Board *English translation of College ter Beoordeling van Geneesmiddelen*
MRP	Mutual Recognition Procedure *European mutual recognition procedure*
OTC	Over-the-counter *This is the pooled legal status of supply GS+PDO+PH; this legal status of supply applies to medicinal products that are available without prescription; also referred to as OTC medicinal products*
NtA	Notice to Applicants
OTC	Over-the-Counter *another name for over-the-counter medicinal products*
QR	Quick response
QRD	Quality review of documents
RMS	Reference Member State *an EU member state that is responsible the assessment of a particular product*
RVG number	Register Packaged Medicinal Products: Unique Dutch marketing authorisation number of a medicinal product.
RVH number	Unique Dutch marketing authorisation number of a homeopathic medicinal product.
SmPC	Summary of Product Characteristics
PO	Pharmacy Only
PDO	Pharmacy and Drugstore Only
PO	Only on Prescription from doctor or specialist

3. Introduction

The second revision of the 'Guideline on Summary of Product Characteristics (SmPC)' was published in September 2009.

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

3.1 Other documents relevant to the SmPC

Via European Committee (Eudralex)

- Directive 2001/83/EC
- See Volume 2c: Guideline on Summary of Product Characteristics (SmPC) – September 2009 Rev 2.

Via EMA

- Standard formulation of paediatric age categories: *See Paediatric medicine – Application guidance – Information on related scientific guidelines: ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population*
- Annotated QRD template for Centralised procedures: *See Product information –> Product information templates Quality Review of Documents human product-information annotated template (English)*
- Annotated QRD template for national and MR/DC procedures: *(See Product information –> Product information templates - Committee for Mutual Recognition and Decentralised Procedures: Human: Annotated Quality Review of Documents template for mutual-recognition and decentralised procedures)*
- Compilation of Quality Review of Documents decisions on stylistic matters in product information: See Product information – Reference documents and guidelines
- Guideline on the excipients in the label and the package leaflet of medicinal products for human use
- Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products /traditional herbal medicinal products

Via MEB

- MEB 8 Guideline on the excipients in the label and the package leaflet of medicinal products for human use (Dutch translation)
- MEB-13 Nomenclature of pharmaceutical products
- MEB policy regarding patented indications (*see MEB website -> Companies-medicinal products for humans -> Legal basis governing medicinal products*)
- MEB 41 "MEB policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups".

3.2 Combined SmPC

- If the SmPC for all RVG numbers contains the same information (for example, if there are multiple dosages for one product), the MEB considers it useful to combine the SmPC so it is immediately clear that 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. 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.
  However, the information specific to certain dosage(s) may be mentioned in writing, for example: “De volgende informatie geldt uitsluitend voor <productnaam> x mg” (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 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 for the treatment of a specific group or a specific indication. See also Chapter 2, section 4.2.

4. Commentary per section of the QRD template

1 – NAME OF THE MEDICINAL PRODUCT

Also refer to the policy document MEB 13 “Nomenclature of pharmaceutical products”.
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:

Dit geneesmiddel bevat minder dan 1 mmol natrium (23 mg) per <dosis>, d.w.z. in wezen 'natriumvrij' (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:
Dit geneesmiddel bevat x mmol (of y mg) natrium per <dosis>. Voorzichtigheid is geboden bij patiënten met een gecontroleerd natriumdieet. (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 MEB-08 "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

See page on MEB website: MEB policy on patented indications.

When mentioning age categories, the boundaries should always be stated in months or years.

<{X} is geïndiceerd voor gebruik bij <volwassenen> <zuigelingen> <kinderen jonger dan 1 jaar> <kinderen> <adolescenten> <in de leeftijd van {x tot y}> <jaar> <maanden>.> (<{X} is indicated for use by <adults> <infants> <children under the age of 1> <children> <adolescents> <between the ages of {x and y}> <year> <months>.>)

4.2 – Posology and method of administration

User instructions for the doctor or other care professionals are placed in this section. Detailed user 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:
"De werking van [Productnaam] wordt niet beïnvloed door de inname van voedsel. [Productnaam] kan zowel voor, tijdens als na de maaltijd worden ingenomen". (The efficacy of [Product name] is not affected by the intake of food. [Product name] may be taken 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:
"*Het is niet bekend of de werking van [Productnaam] wordt beïnvloed door de inname van voedsel. [Productnaam] dient vóór de maaltijd te worden ingenomen*". (*It is unknown*

whether the efficacy of [Product name] is affected by the intake of 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 example, for simvastatin, the dosage varies from 5 to 80 mg per day. The following sentence can then be included in the package leaflet of the Simvastatin 80 mg:
"De aanbevolen doseringen zijn niet allemaal mogelijk met dit product, er zijn echter ook producten met een lagere sterkte dan 80 mg beschikbaar". (The recommended doses are not all possible when using this product; however, products are available with dosages lower than 80 mg.)

If a patient needs to use a lot of 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 mg may include the following statement:
"De aanbevolen doseringen zijn mogelijk met dit product. Er zijn echter ook producten met een hogere sterkte dan 2,5 mg beschikbaar, waardoor minder tabletten per keer nodig zijn". (The recommended dosages are possible with this product. However, products with a higher strength than 2.5 mg are also available, which means that fewer tablets are needed at a 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.
When mentioning age categories, the boundaries should always be stated in months or years.

4.3 - Contraindications

This section must only contain all circumstances and patient groups in which 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 contraindicated, 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 contraindicated group/class can be provided in section 4.5. However, section 4.5 should clearly state that this refers to contraindicated simultaneous use, with a reference to section 4.3.

4.4 – Special warnings and precautions for use

If serious adverse reactions 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:
Gevallen van…. (ernstige bijwerkingen) zijn gemeld na gebruik van X voor de niet geregistreerde indicatie… (Cases of ... (severe adverse reactions) have been reported following use of X for the unauthorised 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> staat op dopinglijst (<X> is on the doping list)
- Het gebruik van <X> kan een positieve uitslag bij een dopingcontrole tot gevolg hebben. (The use of <X> can result in a positive result in a doping test.)
- Het gebruik van <X> als dopingmiddel kan een gevaar vormen voor de gezondheid. (The use of <X> as a doping agent can pose a health risk).

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

In the event of interactions with food, a cross-reference to sections 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 text lists an interaction with warfarin, this cannot automatically be replaced in the Dutch text with coumadin, authorised for use in the Netherlands. This is because interactions are not the same for coumadin 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. It must include a recommendation regarding whether or not breastfeeding may be continued, only needs to be interrupted temporarily (by pumping and disposing of the milk) or needs to be stopped. 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> heeft geen of een verwaarloosbare invloed op de rijvaardigheid en het vermogen om machines te bedienen." (<x> has no or negligible influence on the ability to drive and use machines.)

4.8 – Adverse reactions

Only adverse reactions 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 adverse reaction because he/she believes there is a causal relationship between use of the substance and the adverse reaction (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*	≥1/10
Common	*Vaak*	≥1/100, <1/10
Uncommon	*Soms*	≥1/1,000, <1/100
Rare	*Zelden*	≥1/10,000, <1/1,000
Very rare	*Zeer zelden*	<1/10,000

Not known: frequency cannot be estimated from the available data
Onbekend: op basis van de bekende gegevens kan de frequentie niet worden vastgesteld

Subsection paediatric population

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

If possible, this information on adverse reactions 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))*

When mentioning age categories, the boundaries should always be stated in months or years.

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, i.e. not only E numbers for excipients listed in the Excipients Guideline.

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 that the following E numbers be included on a voluntary basis:'

6.2 Incompatibilities

This section does not require further commentary.

6.3 Shelf life

In this section, both the expiry date and the in-use shelf life, if applicable, are mentioned in accordance with the Guideline on Summary of Product Characteristics.

If the in-use shelf life is not earlier than the expiry date with resealable packaging/packaging for multiple use, this does not have to be explicitly mentioned in accordance with the 'Note for Guidance on in-use stability testing of human medicinal products'. However, the MEB

believes that this information is important for the patient taking OTC medicinal products. Therefore, since September 2016, the MEB has applied national policy on the in-use shelf life of OTC medicinal products (with legal status of supply GS, PDO, PH) with a resealable packaging. See MEB 6 “Labelling of pharmaceutical products”.

The following standard phrases can be used for OTC medicinal products with a resealable package:

If the in-use shelf life is not earlier than the expiry date, the following text should be included after the expiry date:
"Deze datum geldt ook als de verpakking is geopend". (This date also applies if the package has been opened)

If the in-use shelf life is earlier than the expiry date, the following text should be included after the expiry date:
“Na opening van de <primaire verpakking> nog <XXXX dagen/weken/maanden> houdbaar” (‘After opening of the <primary packaging>, this product will expire in <XXXX days/weeks/months>)

6.4 Special precautions for storage

This section does not require further commentary.

6.5 Nature and content of the packaging <and special requirements for use, administration or implantation>

All authorised package sizes must be included, including bulk packaging that is not sold directly to patients but packaged by the pharmacy. An outer box with smaller packs (multi-unit packs for distribution) does not need to be mentioned, however. Therefore, 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 packaging sizes may be marketed" should be included. This does not require further specification.

The EAV packages are not listed in the SmPC guideline. However, if the EAV package contains the same packaging materials/is the same size as already authorised packages listed in the EU SmPC, this may be mentioned in the national SmPC. An EAV package 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/packaging texts are possible without a MRP variation and via a national article 61(3) procedure.

The European SmPC may state 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 English text should state: “The blister holder is not marketed in all countries.”.

The European SmPC can also include the term “childproof” or “senior-citizen-friendly”.

The MEB is of the opinion that there is no such thing as an entirely childproof package, but only of a deterrent package. Regardless of the term in the European text (child-resistant, childsafe, etc) the MEB only accepts the claim “Moeilijk te openen door kinderen” (Difficult to open by children.)

The term “senior-citizen-friendly” is not accepted in the Dutch SmPC. The term ‘senior’ is subjective and does not provide a proper description of the target group.

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 package 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

In this section, only the authorisation holder may be mentioned.
In line with the policy on adding the symbol ® or ™ to the product name (see MEB-13 Nomenclature of pharmaceutical products), additions such as “Handelsmerk van <xxx>” (Trademark of <xxx>) are accepted in the package leaflet and on the package, but not in the SmPC.

8 – MARKETING AUTHORISATION NUMBER(S)

This section does not require further commentary

9 – DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

This section reports the date the authorisation was granted.
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.

Full revision should only be used if the entire SmPC or sections 4 and 5 are reviewed completely/reassessed or if they still meet current knowledge of the product and active

ingredient(s). (NB: thus, they need not be changed but assessed to determine whether they are still up-to-date.) The text with a full revision, therefore, reads as follows: “Laatste volledige herziening: <datum>, wijzigingen in rubriek(en) [gewijzigde rubriek(en)]” (Last full revision: <date>, changes in section(s) [modified section(s)])

For changes in 1 or more sections, the following text should be used:
“Last partial **change** involves section/the sections [revised section(s)]: [date]”. This is to clearly indicate that there has only been a change in the relevant section(s) and not that the entire section has been revised. For the modified sections, only those sections should be mentioned where indeed a substantive change has taken place.

If changes have been made merely to realign the text with the QRD template, it will mention: “Laatste wijziging betreft de opmaak: [datum]” (The last change concerns the format: [date]). Therefore, no sections need to be mentioned.

<11 – Dosimetry>

This section does not require further commentary.

<12 – INSTRUCTIONS FOR THE PREPARATION OF RADIOACTIVE MEDICINAL PRODUCTS>

This section does not require further commentary.