CBG MEB

MEDICINES EVALUATION BOARD

Policy document

Package leaflet of pharmaceutical products

MEB 5

December 2021

1. Contents

2. Abbreviations and definitions

2D	Two-dimensional
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*
DCP	Decentralised Procedure
EAG	Single Unit Dispensing Suitable Packaging
EAV	Single Unit Dispensing Packaging
EMA	European Medicines Agency
EU	European Union
IGJ	Health Care and Youth Inspectorate
MEB	Medicines Evaluation Board *English translation of 'College ter Beoordeling van Geneesmiddelen'*
MRP	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
QR	Quick Response
QRD	Quality Review of Documents

RMS	Reference Member State *An EU member state that is responsible for the assessment of a particular product*
RVG number	Register Packaged Medicinal Products: Unique Dutch registration number of a medicinal product
RVH number	Unique Dutch registration number of a homeopathic medicinal product
SmPC	Summary of Product Characteristics
PH	Pharmacy Only
PDO	Pharmacy and Drugstore Only
PO	Only on prescription from doctor or specialist
URL	Uniform Resource Locator *The URL is an Internet address that indicates where certain information, such as a file or an image, can be found on the Internet.*

3. Introduction

A description included in the box of medicinal products (a 'package leaflet') provides crucial information for patients about how to use those medicinal products properly. A package leaflet that is easy to read contributes to the correct use of medicinal products. The information in the package leaflet is intended for patients as users of the medicinal product or for the parent or carer and for the pharmacist.

European legislation on the package leaflet is discussed in Directive 2001/83/EC. In the Netherlands, implementation took place in the Dutch Medicines Act and the Medicines Act Regulations. Chapter 7 of the Medicines Act and chapter 4.a of the Medicines Act Regulations deal with labelling and the package leaflet.

This policy document (MEB 5) clarifies the policy for the package leaflet of pharmaceutical products in the Netherlands. This policy is based on the European and Dutch legislation mentioned above.

In Europe, the practical implementation of this legislation has been set out in the QRD template. A template in English, which includes comments and a further explanation, is

available. Information that can already be found in the template will not be reiterated in this policy document. There is also a Dutch translation of the sections and standard sentences. The Medicines Evaluation Board (MEB) tests the compulsory textual information as well as the general readability of the package leaflet. See chapter 5 “Readability”.

3.1 Other documents relevant to the package leaflet

Via the European Commission (Eudralex):

- Directive 2001/83/EC
- Notice to Applicants volume 2c
- Guideline on the readability of the label and package leaflet
- Guidance concerning the Braille requirements for labelling and the package leaflet Article 56a of Directive 2001/83/EC as amended
- Guideline on the excipients in the label and the package leaflet of medicinal products for human use
- Blue Box information for products that are authorised via the Centralised Procedure; see the Annex to the Guideline on the packaging information of medicinal products for human use authorised by the Union
- List of details of national competent authorities to contact for requests of translation exemptions falling under Art. 63.3 of Directive 2001/83/EC and cases of shortages

Via EMA:

- Quality review of documents (QRD templates; both centralised and MRP/DCP [CMDh])
- Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products
- Compilation of QRD decisions on stylistic matters in product information
- Recommendations for the implementation of the exemptions to the labelling and packaging leaflet obligations in the centralised procedure
- Quick Response (QR) codes in the labelling and package leaflet of centrally authorised medicinal products

Via CMDh:

- Quality review of documents MRP/DCP (QRD templates)
- Questions & Answers *(*for example, ‘Product Information/Information on medicinal products’)
- QRD guidance and checklist for the review of user testing results *(see the appendix to D70 Overview Template and to MRP Overview Template)*
- Consultation with target patients groups

  This includes the following:

  - Consultation with target patient groups: meeting the requirements of Article 59(3) without the need for a full test – Recommendation for bridging

- Position paper on user testing of package leaflets
- Article 61(3) procedure
- CMDh Best Practice Guidelines
- CMDh position paper on the use of Mobile scanning and other technologies to be included in labelling and PL in order to provide information about the medicinal product

Via MEB:

- MEB 6 Labelling of pharmaceutical products
- 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 14 Parallel import: marketing authorisation and maintenance
- MEB 16 Duplex marketing authorisation
- MEB 21 Listing of 'abbreviated indications' on the packaging of OTC products
- Advice on readability tests for package leaflets for medicinal products
- Declaration regarding the technical aspects of the readability of the package leaflet for pharmaceutical products for human use
- MEB 41 'MEB policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups'
- MEB policy for patented indications
- QRD templates with reference to the website for Centralised Procedures and MRP/DCP procedures
- Toolkit for a simple package leaflet
  This includes the following:
  - List of patient-friendly terms
  - Sample phrases regarding ability to drive, forgetting to take medication, pregnancy and breast feeding
  - General drafting recommendations

Via Wetten.Overheid.nl:

- Dutch Medicines Act (Gmw)
- Medicines Act Regulations (RGmw)

4. Legal Framework

A package leaflet is inserted in a medicinal product's packaging (Section 69, subsection 2 of the Medicines Act).

When applying for a marketing authorisation, a package leaflet must be submitted (Section 3.7 of the Medicines Act Regulations and Article 8(3)(j) of Directive 2001/83/EC).

Changes to be made in the package leaflet by the marketing authorisation holder must be submitted to the MEB (Section 50, subsection 2 of the Medicines Act).

If it becomes apparent after granting a marketing authorisation that the package leaflet does not meet the requirements that are set out in, by virtue of or pursuant to chapter 7 of the Medicines Act, the marketing authorisation may be withdrawn, suspended or amended (Section 51, subsection 1, preamble and letter f, of the Medicines Act).

The package leaflet must be set out in accordance with the summary of product characteristics (SmPC) (Section 4a.2, subsection 1, of the Medicines Act Regulations and Article 59(1) of Directive 2001/83/EC). This means that, with a substantive change of the SmPC, a new modified package leaflet must be submitted at the same time, if applicable.

The text of the package leaflet must be written in Dutch (Section 4a.3, subsection 1, of the Medicines Act Regulations). Package leaflets in several languages are permitted, provided that a declaration is made that the information provided in all languages is the same (Article 63, paragraph 2 of Directive 2001/83/EC), with the exception of the Blue Box requirements. However, the package leaflet must first and foremost comply with the minimum legal requirements for the information in the information leaflet (including readability) and conform to national policy as laid down for the Netherlands. Please see chapter 7 for more information.

Products accepted via MRP/DCP that will not be marketed in the Netherlands may be authorised without the Dutch product information. For more information, please refer to points 6.3 and 6.4 and to the Policy Document 'Medicines Evaluation Board policy concerning marketing authorisations without Dutch translations of the product information and/or mock-ups'.

In exceptional cases, it is possible that the Dutch package leaflet is not delivered **IN** the package but **WITH** the package. Further information about this can be found in section 6.4 of this document. Reference is also made to the EMA website for further information and the procedure that must be followed for products that are accepted through the Centralised procedure.

The 'Guideline on readability' dictates that a package leaflet aimed specifically at that product must be drafted for every product. If the package leaflet is submitted to the MEB for approval, package leaflets for different strengths may combined into a single document, where the information that is specific to certain strengths may be specified in words, such as: 'The following information applies exclusively to <product name> x mg'. The SmPC and the package leaflet must be combined or split in the same manner. The general rule is: The package leaflet follows the SmPC.

In general, all strengths/pharmaceutical forms listed in the SmPC must also be listed in the package leaflet. Even if a product has been authorised in the Netherlands, but not yet marketed. In this latter case, the following standard sentence is used in section 6: “Not all strengths/pharmaceutical forms will be marketed”. If a strength or pharmaceutical form is marketed at a later stage, this sentence in the package leaflet can be amended or deleted.

5. Readability

5.1 General

Section 4a.3, subsection 1, of the Medicines Act Regulation specifically stipulates that the package leaflet must be easy to read for the user and must be worded in simple language. This is explained in greater detail in the 'Guideline on readability'. This means that literal translations from English will not always be approved and adjustments can be made to improve readability, provided that the content remains the same.
The package leaflet must be easy for users both to read and understand. The Toolkit for a simple package leaflet on the MEB website contains tips and tools to a create a package leaflet in Dutch that is easy to understand. The Toolkit also includes a List of patient-friendly terms.

5.2 Readability test

The MEB evaluates the readability of the package leaflet to ensure that the information from the SmPC that is relevant to the user is included in the package leaflet in a patient-friendly manner. The readability test (user test) is an aid for testing readability. Methods for setting up a readability test have been described in the 'Position paper on user testing of package leaflets' on the CMDh website.

The readability of the package leaflet must be tested for new applications, renewals and in case of important changes for which the text has not been defined. It is possible to refer to another tested package leaflet with a bridging report (see 'Guidance concerning consultation with target patient groups for the package leaflet' on the CMDh website).

If texts have been defined for an innovator product (for example, with an Article 30 procedure), generic companies must harmonise their package leaflets accordingly. A user test is not deemed necessary in these cases. However, the generic company must demonstrate that the package leaflet meets the requirements for technical readability (see point 5.3).

5.3 Technical readability

Technical readability includes characteristics of the mock-up, which can influence the readability. These include, for example, font type, font size, use of colour, paper format and paper quality. The ‘Guideline on Readability’ has set out requirements and gives advice on technical readability to improve readability.

The 'Technical declaration of readability form' must be submitted for registration in the Netherlands. This form is provided on the MEB website. For a national application, this form can be submitted together with the readability test (for the initial submission or when answering the questions from the 1st assessment round). For a MRP/DCP, this can be submitted during the national implementation. It is not necessary to include a mock-up of the package leaflet.

6. Specific content-based criteria

The package leaflet must be drafted according to the QRD template. This chapter will outline additional criteria and circumstances that may affect the content and layout of the package leaflet. For detailed information on the QRD template, please see Annex 1.

6.1 Information for healthcare professionals

For parenteral medicinal products and other pharmaceutical products that are usually used in hospitals, the package leaflet may contain information for the patient and information for healthcare professionals. The details that are intended for the patient and for the healthcare professionals must be clearly separated from each other. This can be achieved in the form of two separate package leaflets (patient information leaflet and information for professional medical users) but also by including the information for healthcare professionals at the bottom of the package leaflet.

The MEB adopts this approach in the QRD template. If information is provided for healthcare professionals, a note to that effect must be placed at the bottom of the package leaflet by including the following sentence:

<De volgende informatie is alleen bestemd voor artsen of andere beroepsbeoefenaren in de gezondheidszorg.> (The following information is only for doctors or other healthcare professionals.)

If the entire SmPC is supplied, it is sufficient to include the aforementioned sentence and the SmPC itself need not be repeated when submitting the package leaflet to the MEB. However, if only parts of the SmPC are added (as mentioned in the QRD template), they must be included at the bottom of the package leaflet for the patient, with a cross-reference to section 3 of the package leaflet for the patient.

The package leaflet and information for the professional medical users must be included in the secondary packaging. Extra copies (for example, in the form of a tear-off block) may be provided.

6.2 Patented indications

Due to patent rights, the marketing authorisation holder of the generic product may request that the patented indication are not be included in the marketing authorisation and not to be stated in the SmPC and patient information leaflet in the package of a medicinal product.

The removal of information in relation to a patented indication and the inclusion of the standard phrase in the package leaflet falls under the responsibility of the marketing authorisation holder. If the applicant or marketing authorisation holder wishes to remove an indication from the product information due to a patenting issue, the submission of a variation will always be required prior to the removal of this indication.

For further information please refer to the MEB website: 'Patented indication'.

In the case of a conditional marketing authorisation (*handelsvergunning onder nadere voorwaarden*) (with only an English-language SmPC and package leaflet), the foregoing policy does not apply. This is due to the fact that products with a conditional marketing authorisation are not put on the market.

The foregoing policy will apply as soon as a conditional marketing authorisation has been converted to a regular marketing authorisation.

6.3 Preparation for Administration (Voor Toediening Gereed Maken, VTGM) of medicinal products for intravenous (IV) and subcutaneous (SC) administration in the home situation

Instructions must be included in section 3 of the package leaflet for medicinal products that are prepared for administration and administered in the home situation. The inclusion of information on self-administration in the home situation in the approved product information indicates that the MEB has determined a positive benefit/risk balance. Only this way it is part of the approved medicinal product after being approved by the MEB.

The patient 'injects himself/herself' or the patient prepares the medicinal product for administration and administers it via a permanent venous catheter.

The ease of use or feasibility of administration is important in this regard and will be assessed by the MEB. Samples may be requested in order to gain a good impression of the actions that the patient needs to perform. The company can use a test to demonstrate that the preparation for administration can be performed effectively using these instructions. The instructions are included in the package leaflet (and not in the SmPC); after all, patients only see the package leaflet. The instructions for Preparation for Administration (VTGM) and for administration must be clear and complete. Many people are visually oriented, so supporting pictures in the package leaflet can be useful.

The supplied medicinal product should preferably contain all the required materials to prepare the medicinal product. If the package does not contain all the required materials, this should be stated clearly in the product information, including a list of additional materials that are required (because they are not included in the packaging).

6.4 QR code

It is permitted to include a QR code on the packaging and/or in the package leaflet. Annex 2 at the end of this document describes the conditions that must be met for the use of the QR code on the packaging and/or in the package leaflet for products that have been granted a national marketing authorisation. This policy also applies to parallel-imported medicinal products and for marketing authorisations authorised via replica marketing authorisation procedures.

The same approach applies for techniques that have the same function as the QR code.

6.5 Blue box information for the package leaflet

For products that are authorised via MRP/DCP or via the Centralised procedure, additional information may be required nationally in the package leaflet or on the packaging. In the Netherlands, for example, the RVG number falls under Blue Box information for the package leaflet.

For more information, see the website of the CMDh Blue Box requirements.

6.6 Childproof/senior-citizen-friendly packaging

The MEB is of the opinion that no packaging is fully childproof. Therefore, the MEB considers claims of childproof packaging to be misleading.

Still, the packaging can ensure that it takes longer for a child to open the package. Therefore, the MEB accepts the following claim on childproof packaging. '*Moeilijk te openen voor kinderen*' (i.e. *'Difficult for children to open'*).

If, during an MRP/DCP procedure, a childproof claim has been approved to be mentioned on the package, the claim '*Moeilijk te openen voor kinderen*' will be accepted as a translation of '*child resistant*' on the Dutch package:

Regardless of the term in the European established text (child resistant, childproof, etc.), the MEB only accepts the claim '*Moeilijk te openen door kinderen*'. Claims on '*seniorvriendelijke verpakking*' (senior-citizen-friendly packaging) are not permitted. The term '*senior*' is subjective and does not provide a proper description of the target group.

6.7 Doping warning

The MEB does not agree with the inclusion of a 'doping warning' in the national version of the SmPC and package leaflet, as the doping list is not static, and the warnings on doping could result in a false sense of security. Therefore, the following statements or variations thereof will not be approved in 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.)

6.8 Impossible or difficult dosages

If the product information lists a dosage that cannot be achieved with the product concerned, this must be stated in the SmPC and in 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 with this product, but products with a lower strength than 80 mg are also available).*

If a patient has to use large numbers of tablets, capsules, etc. of a product in order to achieve the recommended dose, whilst a similar product with a higher strength is available, this can also be stated in the SmPC and the package leaflet.

For example, the dosage for enalapril maleate varies from 2.5 to 40 mg per day. The following sentence can then be included in the package leaflet of enalapril maleate 2.5 mg: *'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 for 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).*

If a formulation is not suitable for application and/or use for children, this must be stated in the SmPC and in the package leaflet. The following standard phrase can then be used: *'Deze [(vul farmaceutische vorm in, bijv. tabletten)…] [is; zijn] niet geschikt voor kinderen [en jongeren] [tot xx jaar], [omdat …… (vul reden in voor ongeschiktheid, bijv.: deze te groot zijn voor kinderen om door te slikken)].*
Overleg met uw arts of apotheker of er [een (vul andere farmaceutische vorm in, bijv. drank; smelttabletten geschikt voor kinderen) …] beschikbaar is van dit medicijn die wel geschikt [is; zijn] voor kinderen.'

([This; these] [(list pharmaceutical form of product, e.g. tablets)…] [is; are] not suitable for children [and young people] [up to the age of xx], [because ……(state reason for unsuitability, e.g. they are too big for children to swallow)].
Please consult with your GP or pharmacist to see whether [a (list another pharmaceutical form, e.g. liquid; orodispersible tablets suitable for children) …] of this medical product [is; are] available that [is; are] suitable for children.'

7. Special package leaflets

7.1 Package leaflets for more than one country

It is permitted to add package leaflets for more than one country to multi-lingual packaging. The information for one individual language must be provided in the package leaflet as a unified section. Alongside each individual language, reference must be made to which country the information in that particular language is intended for, for example, by the addition of country codes. In multi-lingual package leaflets, the Blue box requirements that only apply to other countries need not be translated into Dutch. For package leaflets combined with Belgium, the Blue box requirements for both countries should be stated in the Dutch-language version.

Multi-lingual package leaflets including countries outside the EEA are only acceptable if the SmPC is identical in all countries involved and complies with the requirements of Chapter V of Directive 2001/83/EC. The labelling and package leaflet must comply fully with the SmPC as it was adopted in the EEA. Member States may require specific additional information to be included in the package leaflet (the so-called Blue box information). This information must be limited to administrative information.

7.2 Marketing authorisations without Dutch translations of the product information or mock-ups

Since medicinal products are not always marketed immediately after authorisation, the MEB has decided to allow exceptions for the submission of the Dutch translations of the product information.

- There is the option of granting a marketing authorisation in the Netherlands for a product that is accepted via an MRP or DCP without having to submit Dutch translations of the product information and mock-ups. In this case the MEB grants a commercial licence under further conditions. During the authorisation procedure, the English (common) SmPC and package leaflet are approved; subsequently, only sections 1 and 7-10 of the common SmPC and sections 1 and 6 of the common package leaflet are adjusted during National implementation in the Netherlands. This contains specific national information. The labelling does not have to be adjusted. The option of not submitting Dutch translations of the product information and mock-ups also exists for products that are already authorised but have not or not previously been marketed in the Netherlands.

- For a product that is accepted via an MRP or DCP without a Dutch translation of the product information or that is accepted via a national recognition procedure, there is the option of granting a marketing authorisation in the Netherlands without submitting mock-ups.

7.3 Dutch package leaflet not IN but WITH the packaging

For products to be administered by professional groups, in exceptional cases, the English language package leaflet may be delivered not IN but WITH the packaging in the case of:

- a critical product that, due to a small number of users, would not become available on the Dutch market if a Dutch package leaflet must be included IN the packaging or
- a manufacturing process in which it is not possible to add a Dutch package leaflet IN the packaging.

If the patient is to administer the product, the Dutch package leaflet must always be included in the package.

The marketing authorisation holder sends the request with argumentation and documentation to NLtranslationexemptionCP@cbg-meb.nl. For the criteria of a critical product, please refer to the EMA document '*Criteria for classification of critical medicinal products'*. The marketing authorisation holder must also explain why a multilingual package leaflet is not possible for multiple countries, for example together with Belgium.

Only after approval by the MEB it is possible for the Dutch package leaflet to be provided WITH the package rather than IN the package.

A request for a temporary waiver of the Dutch package leaflet in the packages, as in the case of shortages, runs via the Medicine shortages and defects notification centre (www.meldpuntgeneesmiddelentekortendefecten.nl).

7.4 Logos and pictograms

The MEB is generally reticent about allowing the use of logos, images, signs and pictograms in the package leaflet. Signs, images or pictograms may only be used for clarification purposes and may not be used instead of the compulsory text. The package leaflet must comply with the Medicines Act. If the addition of logos, images, signs and pictograms is merely a repetition of the information, this does not contribute to the clarity.

In a package leaflet of an MRP/DCP, the pictograms do not form part of the MRP/DCP package leaflet (i.e. the content part of the package leaflet). Pictograms form part of the layout of the package leaflet and therefore fall under the Blue Box concept (this means that it is decided per country whether the pictograms will be accepted).

Pictograms and images must be evaluated by the MEB. Marketing authorisation holders may not add pictograms retrospectively without approval by the MEB. For further information, please also refer to the policy document 'Labelling of pharmaceutical products' (MEB-6).

7.4.1 CE marking

It is permitted that the CE marking for the medical device supplied is included in the package leaflet. As set out in the MDR, the name and address of the manufacturer of the medical device must be included in the instructions for use (IFU) of the medical device. If these instructions for use form part of the package leaflet, this information may be included in the package leaflet. It must be clearly stated that the relevant information applies to the medical device. The MDR stipulates that the name and address of the EC representative must be stated on the label of the medical device. The MEB prefers that this information is listed on the packaging. This information need not be included in the package leaflet. The pictograms of the EC representative and of the manufacturers may not be included in the package leaflet.

7.5 Parallel import and duplex registrations

7.5.1 Parallel import

Parallel import is the importation and subsequent marketing in the Netherlands of a medicinal product authorised elsewhere in the EU or EEA, whilst this medicinal product has also been authorised in the Netherlands.

In package leaflets of products marketed via parallel import, the composition of the section must be in agreement with the information on the label and/or in the package leaflet from the country of origin.

In accordance with Section 48, subsection 2 of the Medicines Act, the parallel marketing authorisation applies for the same indications, contraindications, adverse reactions, dosages, method of use and method of administration as the product that has already been authorised. Therefore, the sections in the package leaflet on indications, contraindications, adverse reactions, dosage, method of use and method of administration must be worded in the same manner.

The other sections of the package leaflet must be similar, preferably identical in words, to the reference product.

NB: Package leaflet texts (as well as the SmPC) form part of an administrative decision by the MEB. Section 11, conclusion of Copyright Law stipulates that there is no copyright on administrative decisions.

If the Dutch reference product also includes information for the professional medical users on the package leaflet, it must be submitted with the parallel application. This must also include a statement that it is based on the latest approved SmPC of the Dutch reference product.

7.5.2 Duplex registrations

A duplex registration is a registration of a product for which the dossier is identical to that of a product that has already been authorised. The wording of the package leaflet must be identical to the package leaflet of the product that has already been authorised (with the exception of the product-specific information such as the RVG number and the marketing authorisation holder). For more information, please refer to the policy document “Duplex Registration” (MEB-16).

7.6 EAV/EAG packaging

EAV/EAG packages (Unit Dispensing Packages / Unit Dispensing Suitable Packages) are intended for hospitals and nursing homes.

If the EAV packaging contains the same packaging materials/size as the already approved packages that are mentioned in the EU SmPC and package leaflet, these can be mentioned in the national package leaflet. An EAV package can be included in the SmPC during the national implementation of an application procedure for marketing authorisation or during a variation in which the SmPC, subject to the condition that the materials/size are in accordance with the packaging mentioned in the SmPC. An MRP variation is not necessary for addition of this information to the package leaflet/packaging text. A national Article 61(3) procedure can be used.

7.7 Package leaflet for the blind and visually impaired

The marketing authorisation holder must ensure that the package leaflet can also be made available on request by patients in formats suitable for the blind and visually impaired.

In the Netherlands, the blind and visually impaired can call the National Package Leaflet Telephone. The patient can then listen to an audio version of the package leaflet and also request the text in another format, such as Braille or large font.

Please also refer to the 'Guideline on the readability of the labelling and package leaflet of medicinal products for human use' by the European Commission for further information about Braille on the packaging and the package leaflet in a format suitable for the blind and visually impaired.

7.8 Package leaflet for children

A paediatric package leaflet is a package leaflet for children in addition to the mandatory package leaflet. This package leaflet is part of the mandatory package leaflet. The aim of the package leaflet for children is to explain the use of a medicinal product in a way that children can understand. The presentation of the package leaflet for children can consist of text that is easy to understand by the target group, or – for example – a cartoon story.

The MEB is hesitant about approving package leaflets for children. For the time being, package leaflets for children are assessed on a case-by-case basis. The following aspects are important in this regard:

1. Safety information must not be omitted from the package leaflet for children;
2. The package leaflet for children must comply with all requirements for a package leaflet, may not conflict with the package leaflet for doctor and pharmacist (SmPC) and may not contain any promotional elements.
3. The package leaflet for children must be tailored to the language and development level of the target group.
4. Since the package leaflet for children forms part of the package leaflet, it also forms part of the compulsory readability test for package leaflets.

It should be borne in mind that a package leaflet for children should be viewed as a supplement to the existing product information and not as a free-standing document.

Annex 1: Information on sections of package leaflet in the QRD template

This annex is included as an addition to the English and Dutch QRD template. The QRD templates can be found on the EMA website.

Clarification is provided per section in the English **annotated** template. The Dutch template only contains translations of section titles, standard sentences and examples (and not the clarification).

The Dutch QRD template follows below, listing remaining points that are not (sufficiently) discussed in the above-mentioned documents. This information is provided in frames.

Package leaflet: information for the <patient> <user>
{(Invented) name, strength, pharmaceutical form}
{Active substance(s)}

- *Please refer to the relevant MEB policy document (MEB-13) for the directives on the nomenclature of a product.*
- *The complete name must be listed here. In other words, the (invented) name, strength and pharmaceutical form. In addition, the active substances must be listed on the next line. The description of the active substances must correspond with the strength as expressed in the name.*

Example 1
Product name: Clopidogrel X 75 mg
Section 2 of the SmPC: Every film-coated tablet contains 75 mg clopidogrel (as clopidogrel besilate)
Description of active substance in the package leaflet: clopidogrel (as clopidogrel besilate)
Example 2
Product name: Risedronate sodium X weekly 35 mg, film-coated tablets
Section 2 of the SmPC: Contains per film-coated tablet 40.17 mg risedronate sodium hemipentahydrate, corresponding with 35 mg sodium risedronate or with 32.5 mg risedronic acid
Description of active substance in the package leaflet: sodium risedronate

- *In a combined package leaflet, the various product names are listed one below the other.*
- *For a longer product name, the advice is to use the term "this medicinal product" instead of the product name in both the titles of the main sections and sub-sections and the text itself in connection with readability.*
- *The introduction of the package leaflet distinguishes between 'taking' (e.g. tablets, drink) and 'using' (for example, parenterals). This must be followed consistently for the entire package leaflet.*

1. WHAT X IS AND WHAT THIS MEDICINAL PRODUCT IS <USED><TAKEN> FOR

- *This section must list both the mechanism of action of the medicinal product and the relevant pharmacotherapeutic group as well as the indications (in patient-friendly terms). A clear distinction should be made between them.*
- *When reporting age categories, the limits must always be mentioned in months or years.*
- *If the company does not include the patented indication in the printed package leaflet, the following must be included in the printed package leaflet*: *'<Product name> contains <substance name> as active substance, which has also been approved for other conditions not listed in this leaflet. Ask your doctor or pharmacist if you have any further questions.'*
- *The following reference to the MEB sites should be included in the printed patient information leaflet, see also QRD template:*
- *'Detailed information on this medicinal product can be found on the MEB website: www.geneesmiddeleninformatiebank.nl.'*
- *For traditional herbal medicinal products, the indication must start with: 'Traditional herbal medicinal product used for …….(proposed indication(s)).' and end with the sentence: 'This application is based solely on traditional use, not on clinical evidence'.*

2. WHAT YOU NEED TO KNOW BEFORE YOU <USE><TAKE> THIS MEDICINAL PRODUCT

When not to use this medicinal product

- *If concurrent use with a particular group of drugs is contraindicated, inclusion of the following sentence in this section is sufficient:*

This medicinal product may not be used at the same time as certain other medicinal products. See also '<Do you use other medicinal products?><Do you take other medicinal products?>'
After all, it would not be informative for the user to name the group of medicinal products or their mechanisms of action.
For example, if section 4.3 in the SmPC indicates 'Concurrent use with strong CYP3A4 inhibitors', the above sentence can be included in the section 'When not to use this medicinal product?' and a list with the medicinal products can be mentioned in the section "<Do you use other medicinal products?><Do you take other medicinal products?>"

When to exercise caution with this medicinal product

- *It is preferable to include a motivation as to why caution is advised (in accordance with the SmPC or general knowledge)*
-

For example, for acetyl salicylic acid: 'Do not take this medicinal product when undergoing a procedure that increases your chance of bleeding. For example, an operation or when extracting teeth, because the bleeding will last longer'.

- *All warnings must be included.*

Only instructions intended exclusively for the professional group (doctor) do not need to be included. Examples: 'Administer with a metal needle only'.

- *Herbal medicinal products and homeopathic products contain alcohol fairly often. If information about this has been included in the SmPC under 'Warnings and precautions', it must also be mentioned in the package leaflet.*

Children <and adolescents up to 18 years of age>

<Do you use any other medicinal products?><Do you take any other medicinal products?>

- *Only clinically relevant interactions must be included. A summary of research on other pharmaceutical products for which no interaction occurs is not relevant for the package leaflet.*
- *If possible, active substances may be combined in order to shorten the list.*

Examples: 'Calcium antagonists (cardiovascular agents, such as amlodipine or nifedipine)'.

What do you have to bear in mind in relation to <food> <and> <,> <drink> <and> <alcohol>?

- *If information has been included in the SmPC under 'Warnings and precautions' or 'Interactions' (for example, with alcohol or grapefruit juice), it must be included in this sub-section. This information can then be omitted from the section 'Use of X in combination with other medicinal products'.*
- *If there is no information in the SmPC, this section can be omitted.*

Pregnancy <and> <,> lactation <and fertility>

- *If no information about pregnancy, lactation and/or fertility has been included in the SmPC, no additional information needs to be included other than the standard QRD sentence.*
- *If there is no specific information available for pregnancy, breastfeeding or fertility, no mention of this is required in the package leaflet and the heading can be adapted accordingly.*

Effects on ability to drive and use machines

- *Also consider adverse reactions such as dizziness, visual disturbances, drowsiness, and so on.*

The adverse reactions that may be listed here should logically correspond to the adverse reactions listed in the SmPC.

<X contains {name of the excipient(s)}.>

3. HOW TO <USE THIS MEDICINAL PRODUCT> <TAKE THIS MEDICINAL PRODUCT>

- *Duration of use:*

In addition to the Annotated QRD template, information from the SmPC concerning the duration of use must be listed here. Examples:
- For chronic diseases, it is recommended to indicate that the product will be used for a long time.
- For antibiotics, it may be important to indicate the duration of the course and that the course must be completed.

- *A sentence about the duration of action must be included in this section and not in section 1 ('What this medicinal product is <used><taken> for').For example, 'It starts to take effect after about 1 hour and lasts for 6 hours'.*
- *If the product information lists a dosage that cannot be achieved with the relevant product, this must be stated in the SmPC and in the package leaflet, see Chapter 4.10. The following is an example:*

"The recommended doses are not all possible with this product, but there are also products available with a lower strength than <x> mg".

"The recommended dosages are possible for this product. However, there are also products available with a higher strength than <x> mg, requiring fewer tablets at a time".

<Use in children <and adolescents up to 18 years of age>>

<If you <use><take> more of this medicinal product than you should>

- *If specific advice has been included in section 4.9 of the SmPC concerning excessive use of the medicinal product, this must also be stated here. For example, if the SmPC lists a possible treatment as 'induce vomiting', this instruction must also be stated in the package leaflet. For instructions such as 'induce vomiting', add a time indication: 'Induction of vomiting is most effective shortly after ingestion of the medicinal product, no more than 1 hour after ingestion'. The instruction 'DO NOT induce vomiting' is also important for certain products and must of course be included where necessary.*

(Please note that, if nothing is listed in section 4.9 of the SmPC about 'inducing vomiting' and the marketing authorisation holder lists 'induce vomiting' as a treatment in the package leaflet, this must <u>not</u> be accepted.)

- *A package leaflet with EU-agreed wording sometimes states that one should contact a specific treatment centre (for example, the nearest toxicological centre). In the translation to the national package leaflet, this must be replaced with 'nearest emergency care department'.*

<If you forget <to use> <to take> this medicinal product>

<If you stop <taking> <using> this medicinal product>

- *In the case of antibiotics, indicate why the patient must finish the course: '…if not all bacteria are killed, the symptoms may return.'*
- *Indicate that the user must not stop on his/her own initiative: 'Always consult your doctor if you are considering stopping <taking><using> this medicinal product'.*
- *If the user may not stop suddenly, this must be stated here, for example: 'You should not suddenly stop taking this medicinal product; you may experience…. Consult your doctor to gradually decrease the dose'.*
- *This section is not necessary for some products: for example, medicinal products for single use, such as diagnostic agents.*

4. POSSIBLE ADVERSE REACTIONS

- *The layout of this section is important. Use bullet points for the sake of clarity.*
- *It is useful – where applicable – to indicate whether an adverse reaction only occurs at the start of the treatment and then disappears or whether the adverse reaction only occurs after extended treatment.*
- *The following terminology should be used for the **frequencies.** Signs such as < and > are not clear to a patient and must be replaced with more patient-friendly terms.*

*Very common may affect more than 1 in 10 users**
Common may affect up to 1 in 10 users
Occasional may affect up to 1 in 100 users
Rare may affect up to 1 in 1000 users
Very rare may affect up to 1 in 10,000 users
Not known the frequency cannot be estimated from the available data
** a choice can be made between 'users' and 'patients' based on the product.*

- *In general, all adverse reactions listed in the SmPC must also be listed in the package leaflet. When listing the adverse reactions in the package leaflet, it is sometimes possible to list various adverse reactions under one term. For example, various heart rhythm abnormalities can be summarised as 'cardiac arrhythmias'.*
- *The patient-friendly description can be followed by the medical term in brackets, for example: 'tight, painful sensation on the chest (angina pectoris)', particularly for long descriptions of the adverse reaction. This should not be done if a patient-friendly synonym is available: for example, for constipation only list the term "constipation". Please also refer to the List of patient-friendly terms of the MEB.*
- *If an adverse reaction is not immediately recognisable for a patient, the symptoms must be described, which will make the adverse reaction recognisable for the patient. Please also refer to the List of patient-friendly terms.*

- *Examples of adverse reactions that **do** have to be included:*

- Blood count abnormalities; these cannot be recognised immediately by a patient, but can be recognised if the symptoms are described.
- adverse reactions that occur very rarely but are severe, such as anaphylactic shock.

- adverse reactions such as sudden cardiac death and a risk of suicide. It is very important to indicate the frequency here. Listing these adverse reactions could have a negative effect on therapy compliance. However, it is important to include these adverse reactions for liability reasons and in order to provide complete information to patients.
The following formulations are used for these adverse reactions:
- Sudden cardiac death: 'Very rare cases of sudden cardiac arrest have been reported.'
- Risk of suicide: 'There have been very rare reports of patients who developed a tendency towards suicide (e.g. for antidepressants at the start of the treatment). You are advised to contact your doctor immediately if you think that this applies to you.'

- *Examples of adverse reactions that **do not** have to be included:*

- Increase in laboratory values, such as liver enzyme values, without clinical symptoms (not immediately recognisable by the patient).
- Adverse reactions for which a causal link has not been demonstrated.
- Adverse reactions that are not clinically or statistically relevant. This refers to adverse reactions that are listed in the SmPC as having a frequency of occurrence that is not statistically different from a placebo and adverse reactions that occur very rarely and are not severe.

<Additional side effects that may occur in children <and adolescents up to 18 years of age>>

Reporting of adverse reactions

5. HOW TO STORE THIS MEDICINAL PRODUCT

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

If the in-use shelf life is not shorter than the shelf life of resealable packaging/packaging for multiple use, this need not be mentioned explicitly in accordance with the 'Note for Guidance on in-use stability testing of human medicinal products'. However, the MEB is of the opinion that this information is important for patients using OTC medicinal products. Therefore, since September 2016, the MEB has applied national policy on 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 must be included after the expiry date:
'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 must be included after the expiry date:

'After opening of the <primary packaging> this product will expire in <XXXX days/weeks/months>'0.

6. CONTENTS OF THE PACKAGE AND OTHER INFORMATION

What substances this medicinal product contains

<- The active substance(s) in this medicinal product is (are)…>

- *Indicate the active substance and the quantity,*
- *The MEB prefers the listing of both the active substance and the quantity, for example: 'The active substance is minocycline. This is present in the form of minocycline hydrochloride, corresponding to 100 mg minocycline'.*

<- The other substance(s) <(excipient(s))> in this medicinal product is (are)…>

- *In terms of excipients, only the substances need to be listed.*
- *If E numbers are listed in the SmPC, the E numbers must also be included in the package leaflet.*

What X looks like and how much is in a package

- *Describe what medicinal product and package look like, e.g. the tablet and/or bottle, as well as how many units are in a package. The packaging material does not have to be mentioned.*
- *If not all the package sizes authorised in the Netherlands will be marketed, the following standard sentence must be used in section 6: 'Not all strengths/pharmaceutical forms will be marketed.'*
- *The European package leaflet may state that a blister holder has been added to the packaging. The blister holder is designed to carry a single blister strip instead of several blisters (blister strips). This can be indicated using – for example – the sentence: 'The package contains blisters and a blister holder'. As with the package sizes, the leaflet must state: 'The blister holder is not marketed in all countries'.*

Marketing authorisation holder and manufacturer

- *According to the Medicines Act, the party responsible for marketing the product must submit the application for registration in the register. This means that the person or legal entity listed in the package leaflet is the marketing authorisation holder. Examples of contact options are: correspondence address, telephone number, fax number, e-mail address.*
- *The following applies to the address (including the correspondence address): a PO Box (plus city) is not acceptable. This cannot be considered an address in a legal sense. The listing of the address must therefore consist of a street + street number (plus city). The*

country name 'The Netherlands' does not have to be added here, provided that the city is located in the Netherlands.

- *The telephone number listed on the packaging must be the general telephone number for the marketing authorisation holder, with which anyone can get in touch. Listings of special telephone numbers that redirect the caller from the marketing authorisation holder to special 'patient information programmes' or 'patient support programmes' are not permitted.*
- *For the sake of completeness, it is pointed out that it is permitted to provide an alternative address for information and correspondence (and the accompanying representative), in addition to that of the marketing authorisation holder. Whether the marketing authorisation holder is located in the Netherlands or abroad is not relevant. Especially if the marketing authorisation holder is not based in the Netherlands, this information in addition to that of the marketing authorisation holder may make correspondence and the provision of information easier.*
- *The name of the distributor may not be listed in the capacity of 'distributor' because the distributor must be viewed as a wholesale supplier and therefore carries no responsibility whatsoever for the marketing of the product. An exception applies if the marketing authorisation holder, whose contact details are listed in order to serve as 'alternative address for correspondence and information', by coincidence also has the role of distributor. This representative may then of course be mentioned by name, however only in his role as 'representative for correspondence and information'. The role of the representative for correspondence and information must therefore be stated clearly, preceded by the name of this representative (see above). It is not permitted to list the capacity of 'distributor' explicitly, as the term distributor creates confusion about who is responsible for marketing the product. In other words, whether this responsibility is included in the capacity of distributor or not (this is not the case).*
- *In line with the policy of adding the symbol ® or ™ to the product name (see Annex 1, section 1 above), additions such as 'Trademark of <xxx>' are accepted in the package leaflet and on the package, but not in the SmPC.*
- *It is not permitted to list chemists or a licence holder on the trade packaging, as the Medicines Act does not offer scope for this. The Medicines Act does provide the opportunity to use a name for a medicinal product in which an* authorised *brand has been included (other than the marketing authorisation holder). This brand could be the name of a chain of chemists or a licence holder, assuming that they are the marketing authorisation holder for that brand.*
- *Only the logo of the marketing authorisation holder may be added, not the manufacturer's, importer's, licensor's or another company's.*

The following sentence must be included for the Netherlands:

"This medicinal product is listed in the register under <RVG><RVH><EU> number"

- *The RVG number (RVH number for homeopathic products) must be included in section 6.*

The marketing authorisation number consists of the designation RVG or RVH (capital letters, no full stops between the letters) followed by a number. However, for products authorised *via the Centralised Procedure, the letters 'RVG' or 'RVH' are not included in the number of the marketing authorisation. In that case, the number starts with the designation EU/1/… for human medicinal products and with the designation EU/2/… for veterinary medicinal products.*

If a product has a combined number, for example RVG 08916//104217 or RVG 55595=03869, the entire number must be listed in the package leaflet.

<This medicinal product is authorised in member states of the EEA under the following names:>

- *The product name in NL must also be stated here*
- *Countries must be listed in Dutch*

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

- *To be completed by the MEB upon approval/registration.*

<Other information sources>
The following sentence must be included:
'More information on this medicinal product can be found on the MEB website (www.cbg-meb.nl)'

Additions of patient associations are for national implementation. These are not allowed in the leaflet in the Netherlands.

<The following information is only for doctors and other healthcare professionals.>

- *See Chapter 4 'Specific points', section 4.1 'Information for healthcare professionals'*

Annex 2: QR code

Introduction

The QR code (quick response code) is a two-dimensional barcode. The QR code presents a URL for a website. The URL is encoded and printed on the outer packaging of a medicinal product and/or in the package leaflet. A QR reader (application) on a smartphone, for example, is used to scan the QR code. The application translates this scan to the URL and the device's browser opens the relevant website. This provides access to (digital) information about a certain medicinal product.

The policy for the QR code in the Netherlands that is described below applies to all medicinal products that will be or have been awarded a national licence. This policy concurs with the policy as set out in the CMDh for products in the mutual recognition procedure (MRP) and Decentralised Procedure (DCP). The policy also applies to parallel-imported medicinal products and to marketing authorisations awarded via derived authorisation procedures.

This policy only concerns the use of QR codes that refer to web pages containing links and videos with information about the relevant medicinal product. 2D barcodes that are used exclusively for internal production processes and that do not contain information about the medicinal product do not fall under the scope of this policy. The same approach applies for techniques that have the same function as the QR code.

Please also see the 'CMDh position paper on the use of Mobile scanning and other technologies to be included in labelling and PL in order to provide information about the medicinal product'.

Conditions for use of a QR code

In order to place a QR code on the packaging and/or in the package leaflet, the conditions listed in Section 69 of the Medicines Act, the policy document 'Labelling of pharmaceutical products' (MEB 6) and/or the policy document 'Package leaflet for pharmaceutical products' (MEB 5) must be met. This means that the QR code and the underlying information must not contradict the approved Summary of Product Characteristics, must be useful for the patient and must not promote the medicinal product. The content may not include public advertisements.

The following information can be stated below the QR code (called the 'positive list' for the QR codes):

- mandatory product information, such as the information in the SmPC, package leaflet and labelling
- information in relation to pharmacovigilance, such as educational material.

The format in which the information is provided can be determined freely, provided that the conditions for the information underlying the QR code have been met.

The information from this positive list is made available via the QR code by the marketing authorisation holder. The marketing authorisation holder ensures that this information is kept up to date on the relevant website.

A QR code can be included on the packaging and in the package leaflet, on condition that this is secondary in prominence and position to the mandatory information that must be stated on the packaging. In the case of small packages, the QR code can also be positioned on the inside of the packaging. Multiple barcodes can be placed on the packaging, but this may not compromise the readability of the information required by law.

In order to draw patients' attention to the potential differences between the most recently approved product information and the printed package leaflet, the following sentences must be stated in the package leaflet:

'Detailed and up-to-date information for this medicinal product can be obtained by scanning the QR code with a QR reader, an application (app) for smartphone or tablet. The same up-to-date information about the medicinal product is also available via the following URL: <…> and on the website of the Medicines Evaluation Board.
(www.geneesmiddeleninformatiebank.nl)'.

These sentences must be included at the end of the package leaflet (as the last sentences).

The complete URL referring to the QR code is stated next to the QR code. That way, patients who are unable to scan a QR code will have access to the information as well.

The listing of the QR code is not dependent on the legal status of supply and can be used both for medicinal products that are only available with a prescription and for medicinal products that are available without a prescription.

Procedure for inclusion of a QR code

When applying for a marketing authorisation, the applicant must submit a declaration stating that the QR code meets and will continue to meet all the set requirements. For a DCP or MRP procedure, the declaration must be submitted no later than D106. In the case of a national procedure, the applicant must submit the declaration in the second round at the latest. After these points in time, a declaration will no longer be accepted during the procedure of an application for a marketing authorisation.

By submitting this declaration, the applicant confirms that the content of the QR code conforms and will continue to conform to the relevant regulations. If a marketing authorisation has already been awarded for a medicinal product, an Article 61(3) notification can be submitted for the addition of a QR code. Furthermore, the addition of a QR code can also be submitted in combination with another change in the product information in a type IB or type II variation of the C category or during a reauthorisation.

In the case of parallel-imported medicinal products, the QR code of the original applicant for the medicinal product must be covered with tape.

Documentation for submission

The following documentation must be submitted when applying for a QR code on the packaging and/or in the package leaflet:

1. Completed declaration for the QR code:
   a. For MRPs/DCPs: 'Appendix 2 - Applicant's declaration template' (http://www.hma.eu/90.html)
   b. For national procedures: 'QR code declaration' (can be found on the MEB website, https://english.cbg-meb.nl)
2. Full-size mock-ups of the packaging and/or the package leaflet (depending on where the QR code is displayed).
3. Package leaflet: Take into account that the following text must be included:

"Detailed and up-to-date information for this medicinal product can be obtained by scanning the QR code with a QR reader, an application (app) for smartphone or tablet. The same up-to-date information about the medicinal product is also available via the following URL: <…> and on the website of the Medicines Evaluation Board (www.geneesmiddeleninformatiebank.nl)".