COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Policy document

National implementation of additional risk minimisation measures

MEB 45

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Contents

1 Background

1.1 What are additional risk minimisation measures?

The marketing authorisation holder establishes a risk management plan (RMP) for each new medicinal product for which a marketing authorisation is issued. In this RMP, the marketing authorisation holder describes in detail the actions necessary to identify, characterise and avoid risks when using the medicinal product.

The measures proposed by the marketing authorisation holder to minimise these risks are called risk minimisation measures (RMM). In the public assessment report, the assessment authority indicates the measures needed for the safe use of the medicinal product, as well as the reasons why these measures must be taken.

Routine risk minimisation measures (rRMM) are defined for all medicinal products in the Summary of Product Characteristics (SmPC), the patient information leaflet (PIL), the labelling, the package size and the legal status of supply. Routine risk minimisation measures suffice for most medicinal products.

However, *additional* risk minimisation measures (aRMM) are sometimes required to manage the risks and/or strengthen the positive benefit-risk profile of a medicinal product. These measures can be educational or advisory or more about risk management/control. Such aRMM can be imposed as a condition for a marketing authorisation, e.g. from the moment a medicinal product is authorised, but they can also be determined at any time after authorisation. For example, based on new important safety information about the medicinal product.

Examples of aRMM are:

- educational material for doctors, pharmacists and/or patients;
- pregnancy prevention programmes;
- patient cards;
- a controlled access or controlled distribution programme (see Section 7).

General information about aRMM can be found in the *GVP Module XVI Risk minimisation measures (Rev. 3)*[1].

For medicinal products authorised via the centralised procedure (CAP), aRMM are described in the RMP, and aRMM are established in *Annex IID Conditions and restrictions with regard to the safe and effective use of the medicinal product*. These conditions are also included in the European Public Assessment Report (EPAR) for the medicinal product, on the website of the European Medicines Agency (EMA).

For medicinal products registered via the Mutual Recognition Procedure (MRP), the Decentralised Procedure (DCP) or the national procedure, aRMM are described in the RMP, and aRMM are established as conditions for the marketing authorisation. They are also described in the Public Assessment Report (PAR). In cases where aRMM are defined in the RMP but not published in a PAR or End of Procedure letter, the RMP describes the *key elements* that must be included in the additional risk minimisation material.

The aRMM are established for each individual medicinal product, because risks, patient population, relevant target groups and recommendations for reducing or preventing risks can be different.

1.2 National implementation

The marketing authorisation holder may market an authorised medicinal product in the Netherlands after the MEB has approved the aRMM and agreements have been concluded on the distribution of additional risk minimisation material. Additional risk minimisation material must not be printed and distributed in accordance with a distribution plan until it has been approved by the MEB.

aRMM are implemented at the national level through a separate national procedure. This applies to all medicinal products that are marketed in the Netherlands, regardless of whether the marketing authorisation for the product was obtained through a CAP or through an MRP/DCP. The MEB will assess a Dutch version of the aRMM.

There is no need for agreement on the national implementation of aRMM in European committees such as the PRAC, CMDh or CHMP. As a result of the national assessment, the final risk minimisation

[1] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

materials may therefore differ from one European Member State to another because amendments may need to be made to the national situation. In this way, taking the input of healthcare providers and patients at the national level into account in the development of the materials is also encouraged.

2 Scope of this policy document

This document describes how the marketing authorisation holder must develop and distribute additional risk minimisation measures. The document also explains how the MEB assesses the proposals. This policy document is based on current knowledge.

The applicant or marketing authorisation holder may only deviate from this policy document for a clear reason, after having consulted the MEB and obtained the MEB's approval.

Assessment of the Direct Healthcare Professional Communication (DHPC) and assessment of the effectiveness of the risk minimisation materials are beyond the scope of this document.

3 General guidelines

3.1 Documents for assessment

The marketing authorisation holder must submit the following documents to the MEB:

- the Dutch text of the additional risk minimisation material in **MS Word format**;
- screenshots of the website where the additional risk minimisation material will be published online, as well as the URL (direct link) that will be used for this purpose (see Section 6.1);
- a distribution plan, including the target groups, for the additional risk minimisation material;
- the accompanying letter for the healthcare providers if the material will be actively distributed (see Section 8 and Appendix V);
- the proposal for the layout of the Dutch material (the mock-up) in **PDF format**;
- the accompanying letter for the MEB describing the reasons for submitting the additional risk minimisation material. If the marketing authorisation holder proposes changes to the additional risk minimisation material already approved, it must describe the reasons for the changes in this accompanying letter;
- if the marketing authorisation holder is proposing changes to additional risk minimisation material already approved, two versions of the Dutch text of the revised risk minimisation material: a clean version and a version with track changes, both drawn up in MS Word (see Section 9);

- where applicable, a description of the controlled access programme or controlled distribution system (see Section 7).

A PDF of the final version of the additional risk minimisation material, without an accompanying letter, published on www.geneesmiddeleninformatiebank.nl (GIB), the information database operated by the MEB. Make sure that the material does not contain any personal data. Personal data include names and signatures, but also email addresses, for example. Under the GDPR, email addresses from which the name of an employee can be derived in full are not allowed. Therefore, the marketing authorisation holder should use an email address that does not contain any personal data, such as departmentname@organisation.tld, or even an email address that only contains abbreviations: (first letter of first name) (first two letters of surname)@organisation.tld. Using this type of abbreviation makes it harder for outsiders to trace the email address back to a natural person.

3.2 How to submit the documents to the MEB

The documents should be submitted to the MEB in the same way as other documents that require assessment. Information about this can be found on the MEB website: https://www.cbg-meb.nl.

If, as a marketing authorisation holder, you have any questions about the further processing of the aRMM submitted or about the progress being made in the assessment thereof, you can contact us by email (case@cbg-meb.nl), stating the case number in the subject line.

The aRMM can be submitted once the CHMP has issued a positive opinion (for CAPs) or once you have received the CMD(h) conclusion ('End of Procedure' letter) (for MRP/DCP). For medicinal products that are completing an authorisation process through the Centralised Procedure, there is no need to wait until the European Commission Decree has been issued.

If aRMM are imposed on a medicinal product that has already been authorised for the Dutch market, the proposed aRMM must be submitted to the MEB **no later than two months** after the CHMP opinion/CMD(h) conclusion/Board decision of the procedure in which it was imposed. The same deadline applies when previously approved aRMM must be revised following the outcome of a regulatory procedure.

3.3 Decision period

The MEB confirms receipt of the application for the national implementation of aRMM. The request received is validated. For the validation, the MEB applies 14 calendar days, during which the MEB

checks whether the marketing authorisation holder has submitted all the necessary information. If the validation shows that information is missing, the marketing authorisation holder is given the opportunity to rectify this within 14 working days. This recovery period postpones the validation period for the time the marketing authorisation holder takes to submit the missing information.

The decision period is 60 (30+30) calendar days at most, calculated from the date on which the MEB declared that the application was complete (validation). In the first round, the marketing authorisation holder receives notification of the results of the assessment within 30 calendar days after the starting date. If necessary, a second assessment round of 30 calendar days will follow. For example, if there are any questions or comments about the proposed material in the first round. This means that the assessment of the aRMM can be handled by the MEB within 60 calendar days. If the marketing authorisation holder needs time to answer any questions from the MEB, the decision period will be suspended during that period. If you have any questions about how the assessment of the application is proceeding, please contact the MEB via the contact form or contact the case manager assigned to the case.

3.4 Completing the assessment procedure

If the MEB has approved the additional risk minimisation material, as a marketing authorisation holder, you must submit **the approved material** to the MEB within **7 calendar days**, with the final layout **in PDF format**. You are required to submit the approved materials on time. This is necessary to market the medicinal product for which the marketing authorisation has been issued.

If, as a marketing authorisation holder, you do not submit the approved material on time, you will not meet the obligation. The MEB will inform the Health and Youth Care Inspectorate (IGJ) of this.

The material supplied will be added to the file and published in the Medicines Information Bank on the MEB website. The approved materials will be listed in the Medicines Information Bank after the next periodic update.[2]

Some medicinal products have more than one additional risk minimisation material (for example, one for doctors and one for patients). If there is a change in one of the materials, you must (after approval by the MEB) once again provide, **within 7 calendar days**, ***all materials*** **(i.e. also the materials that**

[2] Materials assessed prior to the establishment of these guidelines for marketing authorisation holders will not be published in the Medicines Information Bank retrospectively.

have not been changed) to the MEB in PDF format in their final layout. This is to facilitate publication in the Medicines Information Bank.

3.5 Additional risk minimisation material for generics/hybrids/biosimilars

Additional risk minimisation material for generics, hybrids and biosimilars must be (and remain) identical to the additional risk minimisation material authorised by the MEB for the reference medicinal product. Only the active component of the medicinal product should be mentioned in these materials. Brand names may not be present in this material. Additional risk minimisation material for generics, hybrids and biosimilars may only deviate from the material used for the reference medicinal product if absolutely necessary.

Risk minimisation material relating to generics, hybrids or biosimilars can be distributed upon request if it is identical to the material relating to the reference product that was actively distributed to the target group (see Section 8).

The material must be available online. The website listing the online material may not contain any commercial information, and the web address must be a direct link to the digital version of the material (see Section 6.1). Deviations from the above can only be made with a good reason.

If the additional risk minimisation material is needed for an active component that is marketed by multiple marketing authorisation holders, it is desirable from the point of view of clinical practice that a single common additional risk minimisation material is developed and implemented. In such cases, cooperation between authorisation holders is expected. The MEB may request marketing authorisation holders to initiate such cooperation and may offer to play a supporting role. The marketing authorisation holders must develop and implement the joint additional risk minimisation material together. One of the marketing authorisation holders will be appointed by the collaborating marketing authorisation holders to serve as a liaison between the MEB and the marketing authorisation holders. The MEB will assess the content of the jointly submitted additional risk minimisation material. Should changes need to be made to the additional risk minimisation material, this should be taken care of jointly as well.

3.6 Additional risk minimisation material for parallel imported medicinal products

If any additional risk minimisation material has been established for the Dutch reference medicinal product of a medicinal product imported in parallel, the parallel import marketing authorisation holder must submit identical Dutch additional risk minimisation material and have it approved by the MEB.

The parallel import marketing authorisation holder must contact the marketing authorisation holder of the Dutch reference medicinal product for the additional risk minimisation material. The marketing authorisation holder of the reference medicinal product must cooperate and provide the additional risk minimisation material to the parallel import marketing authorisation holder. The details of the marketing authorisation holder of the Dutch reference product must be changed to the details of the marketing authorisation holder of the parallel product (see also MEB 14 Parallel import: marketing authorisation and maintenance).

Distribution upon request applies to aRMM for parallel imported products if they are identical to the material relating to the reference product that was actively distributed to the target group (see Section 8).

3.7 Additional risk minimisation material for parallel distributed medicinal products

The MEB advises the parallel distributor to determine whether additional risk minimisation material has been established for the reference medicinal product (in the case of parallel distribution, this is always a centralised registered product) as a condition of the marketing authorisation. This can be done via *Annex IID: Conditions and restrictions with regard to the safe and effective use of the medicinal product*, as published in the EPAR product information of the centrally registered reference medicinal product. If additional risk minimisation material has been established for the reference medicinal product, the parallel distributor must submit identical Dutch additional risk minimisation materials and have them approved by the MEB. The parallel distributor must contact the marketing authorisation holder of the Dutch reference medicinal product for the additional risk minimisation material. The marketing authorisation holder of the reference medicinal product must provide the additional risk minimisation material to the parallel distributor.

See the Q&A about parallel distribution on the EMA website (‘Frequently asked questions about parallel distribution’).

3.8 Copyright

No copyright applies to additional risk minimisation materials.

4 Content of the additional risk minimisation materials

All key elements of the additional risk minimisation material must be included correctly and in full in the Dutch-language version of the material.

Guidelines for the content

1. In order to improve *clarity, consistency and recognisability* of the material:
   a. Make sure that the material is in line with the template and with standard phrases as shown in Appendix I (for healthcare providers), Appendix II (for patients/caregivers) and Appendix III (patient cards) to this document.
   b. Where possible, use only the active component of the medicinal product in all of the additional risk minimisation material for healthcare providers. This applies to innovators as well as generics/hybrids/biosimilars/parallels. Thus, do not use brand names in this material. Deviations from the above can only be made with a good reason.
   c. In additional risk minimisation material for patients and/or caregivers, one single reference may be made to the brand name in combination with the name of the active component of the product if:
      - the product concerned is an innovator product and no registrations for products with the same active component with similar additional risk minimisation material is expected to be granted in the next year. The marketing authorisation holder must ensure that the material is changed to a version in which only the active component is used, before the market exclusivity period expires;
      - additional risk minimisation material applies specifically to this brand and/or pharmaceutical form and does not apply to other products with the same active component.
   d. On the first page of the material, place a 'Summary' (summary of the risk and recommended actions to prevent and/or reduce risk) to convey the key message (see the template in Appendix I of this document).

2. The focus should be on the risks associated with the medicinal product for which the material has been drawn up:
   a. Remove safety information that is not related to the key elements described in the conditions of the marketing authorisation. For example, contraindications, warnings, administration techniques, etc. that are already mentioned in the SmPC/patient information leaflet.
   b. Make sure the additional risk minimisation material is readable and as succinct as possible.
   c. Refrain from listing information obtained from clinical trials.
   d. Also, refrain from including any promotional phrases.
   e. Photographs and/or pictures must serve to support and clarify the text.

3. When additional risk minimisation material is proposed that includes patient information, it is the responsibility of the marketing authorisation holder to ensure that the GDPR is complied with.

4. The additional risk minimisation material must also comply with the following:
   a. State where and how healthcare providers can request new material.
   b. The material must always be available online, and the website must be mentioned. See Section 6.1 for information on material available to the public and online.
   c. Always provide a version number and version date in the material.
   d. Avoid references to literature.
   e. Do not refer to patient associations in additional risk minimisation material.
   f. Make sure that material targeted at patients is written in understandable language. In CEFR terms, use language level B1 where possible. Avoid the use of medical jargon where possible. The toolkit for drawing up a readily understood patient information leaflet contains tips and tools that will help you make materials targeted at patients more readable and more easily understood (https://www.cbg-meb.nl/onderwerpen/hv-patientenbijsluiter/toolkit-voor-een-begrijpelijke-bijsluiter).
   g. For digital materials, such as videos, you should also pay attention to the design and which images are used, for example (Digitally accessible communications and content | DigiToegankelijk). Use subtitles in videos, to make them accessible to a wider audience.
   h. When using colours, make sure there is enough colour contrast, and keep in mind that the materials may also be printed in black and white (WebAIM: Contrast Checker).
   i. If a medicinal product is subject to 'additional monitoring', a specific standard phrase must be included in the material that calls for reporting adverse reactions. This applies for both material for healthcare providers and material for patients (see standard phrase 3 in Appendices I and II to this document).
   j. If a medicinal product is not subject to 'additional monitoring', a standard phrase should be included in the material about reporting adverse reactions to the Netherlands Pharmacovigilance Centre Lareb (see standard phrase 4 in Appendices I and II to this document).

English-language material presented in the latest approved version of the RMP (Annex 6 of the RMP) should not be routinely translated into Dutch. The English-language version is not an obligatory part of the assessment by the Rapporteur/Reference Member State. Moreover, an amendment may be needed at the national level. For example, a different sequence and/or different wording.

One exception to this, for example, is the *patient card* (PC), if this is part of the product information and it has been dealt with along with the QRD in the European procedure, in which the Dutch translation has been established at the European level. However, the approved Dutch PC must be supplied **in PDF format** and in final layout to the MEB (see Section 3) within 7 calendar days for publication in the Medicines Information Bank.

5 Layout and design of the additional risk minimisation material

The Appendices to this document contain templates you must follow when drawing up additional risk minimisation material. In addition, the following points must be observed for the layout and design:

1. The layout and design of the additional risk minimisation material must be in line with the rules that apply to the layout and design of the SmPC, patient information leaflet and labelling. See the *Guideline on the readability of the labelling and package leaflet of medicinal products for human use*.
2. The number of different items of material for each medicinal product for any single target group must remain limited. Carefully consider whether different materials that are intended for one target group can be combined.
3. No logos of marketing authorisation holders or local representatives of the marketing authorisation holder may appear on the material.
4. The patient card should be at most the size of a bank card and at least the size of half a bank card. This can be either folded or unfolded (single fold or Z fold). The patient card must be a separate card, rather than something that can be torn from the patient information leaflet.

6 Guidelines for different types of additional risk minimisation material

The marketing authorisation of the medicinal product describes what type of additional risk minimisation material you should use.

In addition to additional risk minimisation material on paper and online, other forms may be acceptable if there is a clear need for this. For example, audiovisual material can show a complex route of administration that can only be clarified with a video. As a marketing authorisation holder, you must submit arguments for this. The MEB will take this into account in the assessment. All forms of additional risk minimisation material must be made available to the MEB so they can be assessed. The optimum form will be chosen.

6.1 Online additional risk minimisation material

All additional risk minimisation materials must be available publicly and online.

Online additional risk minimisation material must comply with the following:

1. The *content* of the online material is identical to the paper version.
2. Online material must be placed on the marketing authorisation holder's webpage. A web address is used that links directly to the digital version of the additional risk minimisation material of the medicinal product. Having the information published in the MEB's Medicines Information Bank is not enough. The marketing authorisation holder must have a webpage of its own with online additional risk minimisation material.
3. In addition to online materials, the marketing authorisation holder must have a paper version of these materials available. An exception is made when the material cannot be converted into a paper version, such as a video.
4. Where possible, online material on the website must be available in PDF format, with the possibility to print it. The website must also explain how new material can be requested.
5. For the assessment of the online material, the marketing authorisation holder must submit screenshots of the website to the MEB. Furthermore, the marketing authorisation holder must submit the URL (direct link) where additional risk minimisation material will be made available to the MEB. This may be the landing page where the materials of the product are published. The URL must be short, simple and informative (for example, www.productname-info.nl; www.productname-armm.nl) to increase readability.
6. Although it is the responsibility of the marketing authorisation holder to ensure that the materials comply with the Dutch Advertising Code,[3] all online or audiovisual materials must:
   a. contain no other information than what has been approved by the MEB;
   b. contain no links to Internet pages with promotional material.
   c. The commercial website of the marketing authorisation holder may have a link that leads to the specific webpage with the materials, but the webpage with the materials must not have commercial and/or promotional links.
   d. The website with the additional risk minimisation material may not be password-protected.

[3]The Code of Conduct for Pharmaceutical Advertising for the risk minimisation material that has healthcare providers as the target group, and the Code for the Advertising of Medicinal Products to the General Public (CPG) for the risk minimisation material that has the patients as the target group

6.2 QR code linking to online additional risk minimisation materials

The marketing authorisation holder may choose to make additional risk minimisation material targeted to patients or their caregivers available through a QR code on the packaging and/or patient information leaflet. Since the MEB is a believer in making additional risk minimisation materials available through QR codes, it would like marketing authorisation holders to consider including QR codes on their packaging and/or in patient information leaflets. Marketing authorisation holders should also consider adding a symbol or text to the code, e.g. 'Scan me – online information'. The QR code will take the reader to the website with additional risk minimisation material. This may be the landing page of the product.

QR codes can also be added to the material during the assessment procedure for national additional risk minimisation material, but they should not replace the URL in the additional risk minimisation material.

There is a separate procedure for including QR codes on packaging and/or in patient information leaflets, which is subject to the QR policy implemented by the EMA,[4] the CMDh position paper[5] and the MEB.[6] This means the application for permission to include a QR code on packaging and/or in a patient information leaflet is not part of the national implementation of additional risk minimisation material.

7 Other types of additional risk minimisation measures

7.1 Risk-management or control measures

In some cases, more control is needed to manage the risks associated with use of a medicinal product. In such cases, risk-management or control measures can be laid down. These control measures can focus on the traceability of the product's distribution. The control measures may also target the healthcare system or the healthcare provider.

[4] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/mobile-scanning-other-technologies-labelling-package-leaflet-centrally-authorised-medicinal-products_en.pdf

[5] https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_313_2014__Rev.12_2023_10_clean_-_CMDh_position_paper_on_mobile_scanning_technologies.pdf

[6] https://www.cbg-meb.nl/onderwerpen/hv-qr-code

The following are examples of risk-management and control measures as set out in GVP XVI rev 3[7]:

- qualification of healthcare personnel required for prescribing, providing and/or administering the medicinal product, and/or for supervision of administration by the patient;
- accreditation of the healthcare institution and the available equipment and qualified healthcare personnel required for the use of the medicinal product in this institution;
- controlled distribution, in which context the entire distribution chain must be traceable (dispatch of the medicinal product from the production location, all distribution points and the care institution where the medicinal product is provided or administered);
- system for documented exchange of patient information (e.g. results of medical tests) that a healthcare provider is to receive from another healthcare provider;
- inspection of patient certificates of medical interventions required for the medicinal product to be prescribed or provided.

A controlled distribution system refers to a series of measures implemented to ensure that all steps in a medicinal product's distribution chain are followed as specified, down to the very moment the medicinal product concerned is prescribed and/or supplied to the patient. For instance, such measures may be imposed on products that are subject to national legislation designed to prevent misuse and/or off-label use of medicinal products.[8]

With a controlled access programme, certain conditions must be met before a medicinal product can be prescribed or issued to a patient. For instance, a special test or examination, proof of vaccination, informed consent, inclusion in a register, or the medicinal product can only be prescribed or issued by healthcare providers especially registered and authorised to do so, etc.[9]

Where applicable, the components of the controlled access system are outlined in the product's RMP and/or in Annex IID to the marketing authorisation (in case of a CAP). Risk-management measures are adopted at the European level and require further detailing at the national level. The marketing

[7] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

[8] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

[9] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

authorisation holder must submit a national approach to the MEB, based on the adopted components of the RMP and/or Annex IID. This procedure is part of the national implementation of the aRMM.

8 Guidelines for the distribution plan

The distribution plan is where the marketing authorisation holder describes the target groups and the way in which the additional risk minimisation material is to be distributed.

8.1 Target groups

- Take a critical look at which healthcare practitioners (potential prescribers, pharmacists and hospital pharmacists, nursing staff/nurse practitioners, physician assistants, other healthcare providers) or patients must receive the material. Healthcare practitioners also include those in training (both doctors in training and hospital pharmacists in training). Risk minimisation material must be sent and addressed to relevant healthcare providers (by name), as agreed with the MEB. In certain cases, additional risk minimisation material can be distributed to hospital departments or to the heads of these departments, if this can be sufficiently justified.
- A limited distribution to part of the target group (for example, those who actually prescribe) is allowed in exceptional cases. For example, in a small patient population (orphan medicinal products) or for medicinal products with a small market share. Limited distribution may also be needed in a controlled access programme (see Section 7.2) or if there are limitations to prescribing by experienced prescribers as stated in Section 4.2 of the SmPC. When limited distribution is being proposed in the distribution plan, the marketing authorisation holder must describe the method that is to be used in determining the precise target group.

8.2 Distribution of the additional risk minimisation material

The marketing authorisation holder must indicate in the distribution plan how the material is to be distributed: through active distribution or through distribution upon request.

A decision tree for the distribution options is presented in Appendix V to this policy document.

<u>Active distribution</u>
The term active distribution is taken to mean that the defined additional risk minimisation material will be distributed by post to the agreed target groups. This can be done in the following ways:

1. *Accompanying letter with paper material*

The paper version of the material is sent to the defined target groups. An accompanying letter must be sent so that the material for every medicinal product can be introduced to the target group in the same way. The accompanying letter describes how the paper version of the material can be requested. Reference is made to online material, and at least one paper version must be sent as well.

2. *Accompanying letter with reference to online material*
   Distribution of an accompanying letter that refers to a webpage with the online material and has instructions on how to request the paper version. This is the method chosen for material that cannot be distributed on paper (e.g. audiovisual material) or for the active distribution of updates to additional risk minimisation material.

Active distribution is recommended in cases where material on an active component is distributed for the first time or in cases where material is being distributed to a newly agreed target group that has not previously received the material. In such cases, an accompanying letter containing at least one paper version of the material will be sent by post. If material previously sent to an agreed target group has been updated, the distribution of an accompanying letter containing a reference to the webpage with the revised version of the online material and instructions on how to request the paper version of the material will suffice (see Section 10). In some cases, some members of the target group (a previously agreed target group) will only receive the accompanying letter, while other members (the newly agreed target group) will receive both the accompanying letter and the paper version of the material.

<u>Distribution upon request</u>

Distribution upon request means that the marketing authorisation holder has a paper version of the material available, and this material can be obtained from the marketing authorisation holder upon request, but the additional risk minimisation material will not be actively distributed to the agreed target group. The target group will also not receive an accompanying letter referring them to the online material.

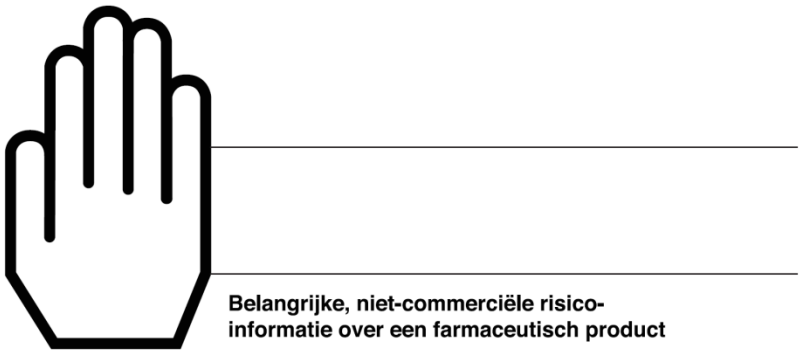
Distribution upon request can be decided if the target group has already been informed about the content of the material about the product and/or active ingredient concerned. For instance, when previously approved and distributed material has been amended (see Section 10 for information about distribution of amended material). Risk minimisation materials relating to generics, hybrids, biosimilars or parallel imported products must only be distributed upon request if they are identical to the material relating to the reference product that was actively distributed to the target group.

Accompanying letter

To ensure the material for every medicinal product can be introduced to the target group in the same way and to improve recognisability, a template has been defined for the accompanying letter to the target group. This template must be used. The template appears in Appendix IV to this document. The accompanying letter contains no logos of the marketing authorisation holders or the local representative of the marketing authorisation holder.

Envelopes

To improve the recognisability of additional risk minimisation material, you must use white envelopes with a white hand logo to send the additional risk minimisation material by post, with the text '*Belangrijke, niet-commerciële risico-informatie over een farmaceutisch product*' (Important, non-commercial risk information about a pharmaceutical product). No other logos may appear on the envelopes, nor any logos of the marketing authorisation holders or local representatives.



	Important, non-commercial risk information about a pharmaceutical product

You can order envelopes with a white hand logo from the VIG association for innovative medicinal products in the Netherlands.

9 Amendments to existing additional risk minimisation material

The marketing authorisation holder must submit already approved additional risk minimisation material for reassessment if:

- the key elements of additional risk minimisation material in the marketing authorisation (e.g. as outlined in RMP Annex 6 or (for CAPs) in Annex IID) have been amended;
- this is recommended during the completion of a procedure (after a CHMP opinion, CMDh conclusion or Board decision);
- new safety information and recommendations have become available on the risk the additional risk minimisation material is supposed to reduce.

If additional risk minimisation material is to be amended, the amended version must be submitted to the MEB no more than **two months** after the end of a procedure (after the CHMP has issued its opinion, the CMDh has issued its conclusion or the Board has issued its decision) (see Section 3).

Please bear the following in mind:

- The marketing authorisation holder must submit justification for the proposed amendments to the previously approved material.
- Materials that have already been approved must be amended in the following update and altered to fit the guidelines and standard sentences as included in the valid MEB 45.
- In addition to a clean version of the Dutch text of the amended risk minimisation material, a version with track changes must also be submitted.
- If a DHPC has been distributed and/or there has been an SmPC update for the same safety issue, the amendments to the risk minimisation materials must be kept in line where possible.
- Limit the number of updates to the material, bundle minor amendments (changes that do not involve the key elements) and editorial changes together over a given period and submit them all together. If various changes are planned for the key elements, they will also be implemented jointly. If you have any questions about the bundling of amendments, please contact the MEB.
- If the marketing authorisation holder or the address details of a centrally registered product change, amended additional risk minimisation material must be submitted in the same way as described in the general guidelines (Section 3). For a non-centrally registered product – provided that these are the only changes – the amended additional risk minimisation material can be sent upon completion of the procedure in which the marketing authorisation holder/address details are amended. The MEB will process the additional risk minimisation material with an appropriate marketing authorisation holder or address data in the Medicines Information Bank.

10 Distribution and redistribution of amended additional risk minimisation material

As a marketing authorisation holder, you must also supply a distribution plan when submitting amended material. It should describe the target groups and the distribution and redistribution of the additional risk minimisation material. The content and assessment of the distribution plan for amended risk minimisation material is done in the same way as described in the general guidelines (Section 3).

10.1 Target groups

When amending additional risk minimisation material, consider whether the already agreed target groups need to be changed, for instance, in cases where a product's indication has been changed.

10.2 Distributing the amended additional risk minimisation material

- For material with a conceptually adapted message to the target group, *active distribution to the agreed target groups* will take place. For example, due to a change in the key elements or amendments to the risk minimisation measures in the RMP that lead to an update. In such cases, briefly describe the changes in an accompanying letter to the target groups (see *Appendix IV Template for accompanying letter*).
- Generally, it is sufficient to inform the previously agreed target groups about the amended material via the accompanying letter without a paper version of the material. The accompanying letter should clearly refer to the website or websites where the amended material is available. If the amendments made to the additional risk minimisation material are substantial, or if the nature of the material has changed, a paper version of the material can be included with the accompanying letter.
- For a newly agreed target group (for example, after an extension to the indications), at least one copy of **a paper version** of the amended material must be actively distributed to the new target group in addition to the accompanying letter with reference to the online material. In some cases, some members of the target group (a previously agreed target group) will only receive the accompanying letter, while other members (the newly agreed target group) will receive both the accompanying letter and the paper version of the material.
- *Distribution upon request* of amended material to the existing target group is acceptable if the amended material has the same message and presents the same measures as the previously distributed version. The marketing authorisation holder makes the amended materials available upon request – or via a web page – after the MEB has assessed and approved it.

A decision tree for the distribution options is presented in Appendix V to this policy document.

11 Deadline for distributing additional risk minimisation material

- Approved additional risk minimisation material for a newly authorised medicinal product must be distributed before the medicinal product is placed on the market, just prior to the planned launch date of the medicinal product. This prevents the period between distribution of the material and the actual marketing of the medicinal product from being too long.
- For the implementation of additional risk minimisation material, the marketing authorisation holder must take the moment its market exclusivity expires into account, to prevent infringement.

- For **new and amended** additional risk minimisation material for an existing medicinal product that needs to be actively distributed to the target group, efforts must be made to distribute the material as quickly as possible. The period depends on the reason for the amendment to the material; this period is defined in the distribution plan. If a new target group has been agreed (e.g. if the range of indications has been expanded), the material must be distributed before the date on which the medicinal product will be launched as treatment for the new indication.

12 Additional risk minimisation material that can be stopped

Additional risk minimisation material can be stopped if it is removed from the RMP and is no longer a condition of the marketing authorisation for the product concerned.

<u>For a centrally registered product</u>
After the amended RMP has been approved in a European procedure, the marketing authorisation holder informs the MEB about the change in the RMP via a separate national procedure (in the same way as described in Section 3.2). After confirmation from the MEB, the marketing authorisation holder will stop distributing additional risk minimisation material, both hard copy and online material. The MEB will remove the additional risk minimisation material from the Medicines Information Bank.

<u>For a non-centrally registered product (national, MRP/DCP)</u>
After the amended RMP has been approved, upon completion of the relevant variation procedure (revision RMP/conditions, mostly C.I.11), the MEB removes the additional risk minimisation material from the Medicines Information Bank. The marketing authorisation holder must stop distributing additional risk minimisation material, both hard copy and material available online.

Appendix I – Template for additional risk minimisation material for prescribers/healthcare providers

1. Standard phrase for the title

State (on the front or title of the material) the target group of the material and the active component. It is recommended that the following be observed as much as possible:

'<type of material> for <target group> on the risks for <active component>'

For example: 'Risk minimisation material for prescribers on the risks of <active component>'

2. Standard phrase on first page

'This material describes recommendations for reducing or preventing important risks of the <active component>. The material is assessed by the Medicines Evaluation Board (MEB).'

3. Briefly describe the indication of the medicinal product

4. Summary

'Summary'

[Point-by-point summary of the risk and the recommended actions to prevent and reduce the risk, to convey the key message (in accordance with the summary in the accompanying letter; see Appendix III). Details are then given in the main text of the material. If Annex IID *Conditions and restrictions with regards to the safe and effective use of the medicinal product* contains a long list of detailed recommendations/actions, the summary can only render a concise summary.]

Where applicable:

'There is extra material for the patient and/or parents or caregivers of the patient. Healthcare providers are requested to provide this material to the patient and/or their parents or caregivers.'

5. Main text of the additional risk minimisation material

[No standard phrases available. The content of the material should follow the guidelines as described above and start with the most important information followed by detailed information.]

6. Standard phrase for reporting adverse reactions

Option 1, for medicinal products covered by 'additional monitoring':

'Report adverse reactions to the Netherlands Pharmacovigilance Centre Lareb
▼ This medicinal product is subject to additional monitoring. As a result, new safety information can be established quickly.

It is important to report suspected adverse reactions after authorisation of the medicinal product. This ensures that the relationship between benefits and risks of the medicinal product is continuously monitored. Healthcare practitioners are requested to report all suspected adverse reactions to the Netherlands Pharmacovigilance Centre Lareb via its website: www.lareb.nl'

Option 2, for medicinal products that are *not* covered by 'additional monitoring':

'Report adverse reactions to the Netherlands Pharmacovigilance Centre Lareb
It is important to report suspected adverse reactions after authorisation of the medicinal product. This ensures that the relationship between benefits and risks of the medicinal product is continuously monitored. Healthcare practitioners are requested to report all suspected adverse reactions to the Netherlands Pharmacovigilance Centre Lareb via its website: www.lareb.nl'

7. Standard phrase used in closing

'Additional material can be obtained from the [department name] department of [marketing authorisation holder], which can be reached on phone number [phone number] or at [email address that does not contain any personal data].
The material can be found online on <URL linking to online material> by scanning <QR code>.
Additional information regarding <active component> can be found in the Summary of Product Characteristics (SmPC) and in the patient information leaflet on www.geneesmiddeleninformatiebank.nl.

Appendix II – Template for additional risk minimisation material for the patient and/or their parents or caregivers

1. Standard phrase for the title

On the front page and/or at the start of the material, state the target group of the material, the active component and, where applicable, the brand name.*

It is recommended that the following be observed as much as possible:

'Information for the <target group (for example, patients and their parents and caregivers)>'
'Take care when using <brand name (active component)> or <active component>.'
Standard phrase if applicable:
'<Active component> is the active ingredient in the medicinal product. Your medicinal product may have a brand name that differs from the name of the active ingredient, so make sure you check carefully to which medicinal product we are referring here.'

2. Main text of the additional risk minimisation material

[No standard phrases available. The content of the material should follow the guidelines as described above and start with the most important information followed by detailed information.]

3. Standard phrase for reporting adverse reactions

Option 1, for medicinal products covered by 'additional monitoring':

'Report adverse reactions to the Netherlands Pharmacovigilance Centre Lareb
▼ This medicinal product is subject to additional monitoring. This ensures that we quickly obtain new information about the safety of this medicinal product.
Please contact your doctor if you experience any adverse reactions. This also applies for any adverse reactions that are not listed in the patient information leaflet. You can report adverse reactions via the Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl. Reporting adverse reactions also provides us with more information about the safety of this medicinal product.'

Option 2, for medicinal products that are *not* covered by 'additional monitoring':

'Report adverse reactions to the Netherlands Pharmacovigilance Centre Lareb

Please contact your doctor if you experience any adverse reactions. This also applies for any adverse reactions that are not listed in the patient information leaflet. You can report adverse reactions via the Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl. Reporting adverse reactions also provides us with more information about the safety of this medicinal product.'

4. Standard phrase used in closing

'More information
This information can also be found at <web address of online material> by scanning <QR code>
Read the patient information leaflet on www.geneesmiddeleninformatiebank.nl for more information on your medicinal product.
If you have any questions about your medicinal product, please consult your doctor or pharmacist.

This material was approved by the Dutch Medicines Evaluation Board (www.cbg-meb.nl).'

* See Section 4.

Appendix III – Template for a patient card that is not part of the product information

1. Standard phrase for the title

On the front page and/or at the start of the material, state the target group of the material, the active component and, where applicable, the brand name.* It is recommended that the following be observed as much as possible:

'Patient card for><Brand name (active component)> or <active component>'

2. Main text of the additional risk minimisation material

[No standard phrases available. The content of the material should follow the guidelines as described above and start with the most important information followed by detailed information.]

If you would like more information about your medicinal product, read the patient information leaflet or scan the QR code to read more information online. If you have any questions about your medicinal product or adverse reactions, please consult your doctor or pharmacist.

3. Standard phrase used in closing

Name of patient and, where relevant, the contact details of their prescriber.

* See Section 4

Appendix IV – Template for the accompanying letter for distributing additional risk minimisation material

If the material is to be distributed actively, the marketing authorisation holder must draw up an accompanying letter to the target group of the additional risk minimisation material. Use the template provided below to do so. The importance of the materials is briefly introduced through the summary of risks and actions in this accompanying letter.

1. Opening of the accompanying letter

'Risk minimisation materials for <target group> on the risks of <active component>'

'Dear Sir/Madam,

In consultation with the Medicines Evaluation Board (MEB), we would like to inform you about additional risk minimisation materials for <active component>, a <type of medicinal product>. These materials contain recommendations that will help you reduce or prevent the significant risks associated with this medicinal product.'

2. Briefly describe the indication of the medicinal product

3. Summary

'Summary'

[Point-by-point summary of the risk and recommended actions to prevent and reduce the risk, to convey the key message (in accordance with the summary on the first page of the additional risk minimisation material for healthcare providers; see Appendix I). Details are then given in the main text of the material. If *Annex IID Conditions and restrictions with regards to the safe and effective use of the medicinal product* contains a long list of detailed recommendations, the summary can only render a concise summary.]

4. For amended additional risk minimisation material only, add the following to the letter:

'The material for <active component> has been amended with:
- information on risk X;
- ....'

Standard phrase if applicable:

'There is extra material for the patient and/or parents or caregivers of the patient. You are requested to provide this material to the patient or their parents or caregivers.'

5. If a paper version of the additional risk minimisation material is included, add the following to the letter:

'Please find the materials enclosed.'

6. Standard phrase on the availability of materials

'Additional material can be obtained from the [department name] department of [marketing authorisation holder], which can be reached on phone number [phone number] or at [email address that does not contain any personal data].
The material can be found online on <URL linking to online material> by scanning <QR code>.
Additional information regarding <active component> can be found in the Summary of Product Characteristics (SmPC) and in the patient information leaflet on www.geneesmiddeleninformatiebank.nl.'

7. Standard phrase for reporting adverse reactions

Option 1, for medicinal products covered by 'additional monitoring':

'Report adverse reactions to the Netherlands Pharmacovigilance Centre Lareb
▼ This medicinal product is subject to additional monitoring. As a result, new safety information can be established quickly.

It is important to report suspected adverse reactions after authorisation of the medicinal product. This ensures that the relationship between benefits and risks of the medicinal product is continuously monitored. You are requested to report all suspected adverse reactions to the Netherlands Pharmacovigilance Centre Lareb via its website: www.lareb.nl'

Option 2, for medicinal products that are *not* covered by 'additional monitoring':

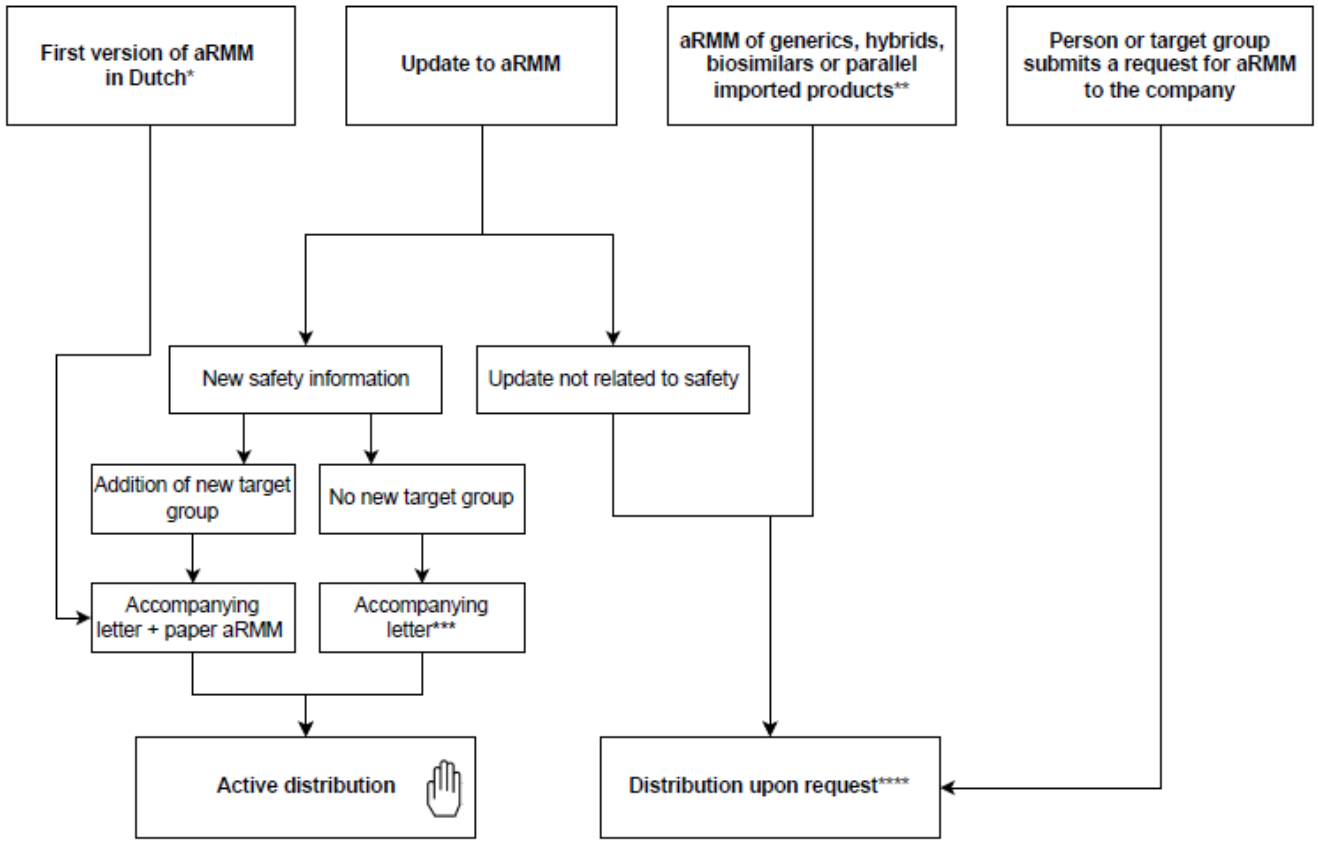
'Report adverse reactions to the Netherlands Pharmacovigilance Centre Lareb
It is important to report suspected adverse reactions after authorisation of the medicinal product. This ensures that the relationship between benefits and risks of the medicinal product is continuously monitored. You are requested to report all suspected adverse reactions to the Netherlands Pharmacovigilance Centre Lareb via its website: www.lareb.nl'

8. Closing

'Kind regards,
[name and signature of authorised person at the marketing authorisation holder]

Enclosures:
- Material for prescribers/healthcare providers;
- Material for patients and their parents or caregivers.'

Appendix V – Decision tree for the distribution of additional risk minimisation material



* If the first version of the additional risk minimisation material concerns only material that cannot be distributed on paper (e.g. audiovisual material), only the accompanying letter presenting the URL of the online material needs to be distributed.

** Additional risk minimisation material for generics/hybrids/biosimilars/parallel imported products that is identical to the material relating to the reference product that was actively distributed to the target group.

*** Generally, it is sufficient to inform the previously agreed target groups about the amended material via the accompanying letter. The accompanying letter should clearly refer to the website or websites where the amended material is available. If the amendments made to the additional risk minimisation material are substantial, or if the nature of the educational material has changed, you can also enclose a paper version of the material.

**** The marketing authorisation holder must have a paper version of the material available for distribution at all times.