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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

PROCEDURE FOR THE PREPARATION OF AN ENTRY TO THE 'COMMUNITY LIST OF HERBAL SUBSTANCES, PREPARATIONS AND COMBINATIONS THEREOF FOR USE IN TRADITIONAL HERBAL MEDICINAL PRODUCTS'

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1. Purpose

The purpose of this document is to streamline and enable consistent preparation of draft entries to the 'list of herbal substances[1], preparations and combinations thereof for use in traditional herbal medicinal products by the EMEA Committee on Herbal Medicinal Products (HMPC).

According to Article 16f(1) of Directive 2001/83/EC as amended, a draft list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products shall be established in accordance with the procedure referred to in Article 121(2). The list shall contain with regard to each herbal substance, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional medicinal product.
This list is hereafter referred to as the 'Community list'.

2 Scope

This procedure applies to all HMPC Rapporteurs/CoRapporteurs for the preparation of draft entries to the Community list.
This procedure does not describe the steps for the identification of priority herbal substances/preparations/combinations to be covered by a list entry.

3 Responsibilities

Rapporteurs/CoRapporteurs must ensure the adherence to this procedure in the preparation of a draft entry to the Community list.
It is the responsibility of the HMPC secretariat and the Chairperson of the HMPC Working Party on Community Monographs and Community List to verify that this procedure is adhered to and related templates are used.

4. Templates needed for this procedure

- 'Template for a Community list entry' (EMEA/HMPC/439705/2006 Rev. 2)
- 'Assessment report template for the development of Community herbal monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the Community list' (EMEA/HMPC/418902/2005)

5. Related documents

- Committee on Herbal Medicinal Products - Rules of Procedure (EMEA/HMPC/139800/2004)
- 'Guideline on the documentation to be submitted for inclusion into the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' (EMEA/HMPC/107399/2005 Rev. 1)
- 'Timetable for the establishment of a Community list entry and/or of a Community herbal monograph' (EMEA/HMPC/126542/2005 Rev.1)
- 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2)
- 'Procedure for the preparation of Community monographs for traditional herbal medicinal products' (EMEA/HMPC/182320/2005 Rev.2)

[1] The term "herbal substance" should be considered equivalent to the term "herbal drug" as defined in the European Pharmacopoeia and the term "herbal preparation" should be considered equivalent to the term "herbal drug preparation" as defined in the European Pharmacopoeia

- 'Public statement on the interpretation of the term "external use" for use in the field of traditional herbal medicinal products' (EMEA/HMPC/31897/2006)

6. Definitions, abbreviations and references

Definitions

Community list entry = document whose purpose is to provide structured information, including information laid down in Article 16f(1) of Directive 2001/83/EC as amended, relating to specific herbal substances or herbal preparations or combinations of substances and preparations from a given plant[2] for use in traditional herbal medicinal products.

Abbreviations

CHMP – Committee for Medicinal Products for Human Use
CPMP – Committee for Proprietary Medicinal Products
EMEA – European Medicines Agency
EWP – CHMP Efficacy Working Party
HMPC – Committee on Herbal Medicinal Products
QRD – Quality Review of Documents Group
QWP – CHMP Quality Working Party
SPC – Summary of Product Characteristics

References

- The rules governing medicinal products in the European Union, Volume 1, Pharmaceutical Legislation
- The rules governing medicinal products in the European Union, Volumes 2A, 2B and 2C, Notice to Applicants
- 'Guideline on Summary of Product Characteristics' (Notice to Applicants, Volume 2C Regulatory guidelines)
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/spcguidrev1-oct2005.pdf
- Product Information Templates, Human Medicinal Products. Quality Review of Documents Group
  http://www.emea.europa.eu/htms/human/qrd/qrdintro.htm
- 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00 Rev.1 and EMEA/CVMP/814/00 Rev.1)
- 'Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC' (EMEA/HMPC/CHMP/CVMP/287539/2005)
- List of standard terms for pharmaceutical dosage forms, routes of administration and containers used for medicines for human and veterinary use (European Pharmacopoeia, EDQM & Healthcare)
  http://www.edqm.eu/site/page_590.php
- 'Guideline on excipients in the label and package leaflet of medicinal products for human use' (Notice to Applicants, Volume 3B Safety, Environment and Information guidelines)
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-3/pdfs-en/3bc7a_200307en.pdf
- 'Note for guidance on the investigation of drug interactions' (CPMP/EWP/560/95)
- 'Guideline[3] on excipients in the dossier for application for marketing authorisation of a medicinal product' (CHMP/QWP/419/03)
- 'Note for guidance on declaration of storage conditions in the product information of medicinal products' (CPMP/QWP/609/96 Rev.1)

[2] It will be indicated if more than one plant is used and if hybrids are also used.
[3] Published as 'Note for guidance on excipients, antioxidants and antimicrobial preservatives in the dossier for application for marketing authorisation of a medicinal product'

7. Records

All documents, including correspondence, will be filed at the EMEA in the corresponding master file (paper documents) and/or electronic file (specific "Community monographs/Community list" folder in "HMPC" folder). The EMEA Secretariat shall track whether documents are available in paper and/or electronic format.
Rapporteur/CoRapporteur shall provide copies of all bibliographic references supporting a monograph/list entry to the HMPC Secretariat, preferably in 2 steps i.e. first the references supporting the draft version released for public consultation, which shall then be completed by the additional references assessed in the post-consultation phase. In any case, a complete set of references shall be received at the EMEA when the HMPC Assessment Report is published on the EMEA website.

The HMPC Secretariat will record various administrative data about each Community list entry. These administrative data are the following:

- Rapporteur and/or CoRapporteur

- Cross-reference to HMPC Assessment Report

- List of references and unpublished data used in HMPC Assessment Report

- Status
  Under evaluation
  Valid (date of HMPC Opinion, date of European Commission Decision)
  Suspended (date of HMPC Opinion, date of European Commission Decision)
  Revoked (date of HMPC Opinion, date of European Commission Decision)
  Subject to a variation/extension

- Numbering
  documentation of past versions with modifications tracking system

- Cross-reference to EU Numbers in EudraPharm[4] Database
  for licensed medicines containing same herbal substance/preparation/combination

8. Instructions

Transfer relevant information from the assessment report into the 'Template for a Community list entry' under the respective headings.

For the title of the Community list entry when referring to [herbal substance/herbal preparation], the name should be recorded as:

> botanical name of the plant according to the binomial system (genus, species, variety and author),[comma] the plant part in Latin. Example: *Valeriana officinalis* L., radix.

In the case where more than one plant is used, all plant names should be mentioned. For example, the title of a Community list entry on Hawthorn Leaf and Flower will be:
Community list entry on *Crataegus monogyna* Jacq. (Lindm.), *C. laevigata* (Poiret) D.C. (*C. oxyacanthoides* Thuill.) or their hybrids, *C. pentagyna* Waldst. et Kit. ex Willd., *C. nigra* Waldst. et Kit., *C. azarolus* L., folium cum flore

[4] EudraPharm (http://eudrapharm.eu/eudrapharm/welcome.do)

For the keywords section of the Community list entry, the botanical name of the plant according to the binomial system, the Latin term for the herbal substance and the common name of the herbal substance in English should be included.

Procedure for the preparation of an entry to the 'Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products'

Scientific name of the plant

Botanical name according to the binomial system (genus, species, variety, author)
Example: *Valeriana officinalis* L.

Botanical family

Common name in all EU[5] official languages

Insert translations of the common name of the plant and the plant part, as provided by MLWP or HMPC members.

Herbal substance(s) or Herbal preparation(s) or Combination(s)

Herbal substance(s)
Define the herbal substance by the botanical name according to the binomial system (genus, species, variety and author), [comma] the plant part used in Latin, followed by, in bracket, the herbal substance name in English.
Example: *Valeriana officinalis* L., radix (valerian root).
Describe more precisely the herbal substance, especially whether fresh or dried.
For examples:
- dried, whole or fragmented bark of the stems and branches
- dried, ripe seeds

Herbal preparation(s)
Herbal preparations should be referred to in English, unless it is preferable to use the Latin name given in the pharmacopoeia of a Member State.
The type of extracts should be specified as defined in the Ph. Eur. general monograph on extracts (ref. 01/2005:0765); indicate the solvent or solvents used for extraction (exact or as a range) and the ratio of the starting material to the genuine extract (DER).
For examples:
- liquid extract (1:4-12); extraction solvent: ethanol 50-80% (V/V)
- dried expressed juice (a-b:1)

Combination(s)
Define them in analogy to herbal substances and preparations.

European Pharmacopoeia monograph reference

Provide reference of relevant European Pharmacopoeia monograph(s) if it(they) exist(s) or reference to the monograph(s) of an official pharmacopoeia of a Member State if available.

[5] Including languages of European Economic Area (EEA) states

Indication(s)

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment, prevention and diagnostic indication.

i) The indication(s) should include the following standard statements:

   a. <Herbal medicinal product traditionally used…..> or <Traditional herbal medicinal product for …..>
   b. [The product is a traditional herbal medicinal product for use in specified indication(s) exclusively based on long-standing use].

ii) Note that only indications intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment are acceptable within the scope of traditional herbal medicinal products.

iii) Target disease or condition(s) to be treated.

iv) Target population, when appropriate.

Type of tradition

State the type of tradition, e.g. European (to be specified), Chinese, Ayurveda or others if necessary to explain the indication.

Specified strength

Provide information on dose range.
Cross-refer to 'Specified posology' where appropriate.

Specified posology

The dosage has to be clearly specified for each method/route of administration and for each indication:

1) For each age category, where appropriate (specify age ranges) i.e. infants, children[6], adolescents[7], adults, elderly:

   a) Specific dose
   b) Maximum recommended single, daily and/or total dose, and
   c) Dosage frequency

2a) 'The use in children <under><above> Y years of age is contraindicated.' (with a cross-reference to 'Contraindications').

2b) If the herbal substance/preparation has not been studied in the paediatric population or if there are insufficient data on which to base an approval for paediatric use, there should be a recommendation that the medicinal product should not be used in the paediatric age group until further data become available (with a cross-reference to 'Special warnings and precautions for use).

[6] Between 2 and 11 years of age
[7] Between 12 and 18 years of age

Route of administration

Indicate the route of administration.
Oral, external and/or inhalation preparations only are acceptable within the scope of traditional herbal medicinal product. Where appropriate, refer to the 'Public statement on the interpretation of the term "external use" for use in the field of traditional herbal medicinal products' (EMEA/HMPC/31897/2006).
The route of administration should be described by the European Pharmacopoeia full standard term[8].

Provide information in relation to:
- the intake of the product in relation to food intake.
- the method of administration and/or relevant instruction for correct administration/use.

Duration of use or any restrictions on the duration of use

Introduce recommendation on duration of use and any related relevant restriction.

When relevant, the following standard statement, as per the provisions in Article 16g(2)(b) of Directive 2001/83/EC as amended, should appear:
<If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.>

Any other information necessary for the safe use

- **Contraindications**

Situations where the medicinal product must not be given for safety reasons.

i) Contraindications including specific patient populations.

The following statement can be used:
<Children <age range to be specified> because <include reason>.>

ii) Other medicines or classes of medicines, which should be specifically avoided (i.e. contraindicated), if applicable a cross-reference to section 'Interactions with other medicinal products and other forms of interactions should be given. In general, patient populations not studied should be mentioned in section 'Special warnings and precautions for use' unless a safety issue can be predicted.

iii) Only if pregnancy is strictly contraindicated, should it be mentioned here. In section 'Pregnancy and lactation', a cross-reference should be given and further information about the background be provided. Contraindication in pregnancy should be supported by human data or by strong nonclinical data.

Hypersensitivity to the <active substance(s)>, extended to other parts of the same plant or possible cross-reactions to other members of the relevant plant family or to any of the excipients, should be described.
The following standard statement should be used when no specific wording is necessary:
<Hypersensitivity to the active substance(s)>.

- **Special warnings and precautions for use**

Conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled.

[8] List of standard terms for pharmaceutical dosage forms, routes of administration and containers used for medicines for human and veterinary use (European Pharmacopoeia, EDQM & Healthcare) http://www.edqm.eu/site/page_590.php

i) In general it should appear in the following order, determined by the importance of the safety information provided:

a) Special warnings
b) Precautions for use.

The following standard statement can be used:
<The use is not recommended in children <age range to be specified> because <include reason>.>

Note that contraindications should be mentioned under 'Contraindications' only and should not be repeated here.

ii) In accordance with the 'Guideline on excipients in the label and package leaflet of medicinal products for human use' (Notice to Applicants, Volume 3B Safety, Environment and Information guidelines), products containing alcohol should carry an appropriate warning based on the total alcohol content. Where alcohol is part of the herbal preparation, e.g. in the case of tinctures, the appropriate warning necessary for excipients or residues from the manufacturing process should be included.

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

Information on the potential for clinically relevant interactions based on the pharmacological properties of the medicinal product.
As relevant as per:

a) 'Guideline on SPCs' (Notice to Applicants, Volume 2C Regulatory guidelines)

b) 'Note for guidance on the investigations of drug interactions' (CPMP/EWP/560/95)

The following standard statement can be used:
<None reported.>

- **Pregnancy and lactation**

i) For examples of pregnancy and lactation statements, see[9] Annexes I and III of the 'Guideline on SPCs'

ii) If pregnancy is strictly contraindicated, further information about the background should be provided. Contraindication in pregnancy should be supported by human data or by strong nonclinical data.

The following standard statements can be used:
<In the absence of sufficient data, the use during pregnancy and lactation is not recommended.>
< Safety during pregnancy and lactation has not been established.>

[9] Also published in the appendix 1 of the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling' (EMEA/CHMP/203927/2005)

- **Effects on ability to drive and use machines**

Where applicable the following standard statements should appear:

<{Herbal substance/preparation} has <no or negligible><minor or moderate><major> influence on the ability to drive and use machines.>
<No studies on the effects on the ability to drive and use machines have been performed.>
<Not relevant.>

For herbal preparations containing alcohol, the appropriate statement in accordance with the 'Guideline on excipients in the dossier for marketing authorisation of a medicinal product' (CHMP/QWP/419/03) should be included.

- **Undesirable effects**

This section should provide comprehensive information based on all adverse reactions[10] (ADRs). Adverse events, without at least a suspected causal relationship, should not be included.
It should be worded in concise and specific language and should state what are the most serious and/or most frequently occurring ADRs.
Any undesirable event warnings necessary for excipients or residues from the manufacturing process should be included.
The expressions isolated/single cases/reports should not be used.
The use of general statement such as "xxx may occur very rarely" is not recommended. ADRs frequency should be estimated from available data and frequency groupings described in the 'Guideline on SPCs' should be used, following the proposed convention, from 'very common' (≥1/10) to 'not known' (cannot be estimated from the available data).
If there is no information on adverse reactions, the following statement should be included:
<None known.>

When relevant, the following standard statement, as per the provisions in Article 16g(2)(b) of Directive 2001/83/EC as amended, should appear:
<If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.>

- **Overdose**

Describe acute symptoms and signs and potential sequelae of different dose levels of medicinal products based on accidental mistakes by patients.

If there is no information on overdose, the following statement should be included:
<No case of overdose has been reported.>

- **Pharmaceuticals particulars [If necessary]**

Where relevant, include information on physical and chemical incompatibilities with other products, special precautions for storage, special precautions for disposal or waste materials derived from such medicinal products.

If there is no information on pharmaceutical particulars pertinent to the safe use of the product, the following statement should be included:
<Not applicable.>

- **Pharmacological effects or efficacy plausible on the basis of long-standing use and experience [If necessary for the safe use of the product]**

Introduce a short description of the main pharmacological effects or the data related to plausible efficacy sustaining the traditional use if necessary for the safe use of the product.

[10] Relevant ADRs references will be listed in the assessment report.