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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

**PROCEDURE FOR THE PREPARATION OF COMMUNITY MONOGRAPHS FOR
TRADITIONAL HERBAL MEDICINAL PRODUCTS**

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1. Purpose

The purpose of this document including its attachments is to streamline and enable consistent preparation of Community herbal monographs by the EMEA Committee on Herbal Medicinal Products (HMPC).

According to Article 16h(3) of Directive 2001/83/EC, as amended as regards traditional herbal medicinal products, the HMPC shall establish Community herbal monographs for traditional herbal medicinal products. According to Article 16h(3), when Community herbal monographs have been established, Member States shall take them into account when examining an application.

According to Article 16c(4) of Directive 2001/83/EC, as amended, the HMPC shall, on the request of a Member State, establish a Community herbal monograph for a traditional herbal medicinal product that has been used within the Community for less than 15 years, if the Committee considers it possible.

The structure of Community monographs has been designed following the Summary of Product Characteristics (SPC) structure, as established by Article 8(3j) of Directive 2001/83/EC. The SPC of a medicinal product sets out the agreed position on the medicinal product as distilled during the course of the assessment process.

The HMPC, when establishing a specific Community herbal monograph for traditional herbal medicinal products, has to review and assess the available information and documentation on the traditional use of a group of herbal medicinal products, even though a Community monograph does not correspond to a specific SPC.

2 Scope

This procedure applies to all HMPC Rapporteurs/CoRapporteurs for the preparation of Community monographs for traditional herbal medicinal products.

3 Responsibilities

Rapporteurs/CoRapporteurs must ensure the adherence to this procedure in the preparation of a Community monograph for traditional herbal medicinal products.

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 herbal monograph' (EMEA/HMPC/107436/2005 Rev.2)
- 'Assessment report template for the preparation 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 list of herbal substances, preparations and combinations thereof' (EMEA/HMPC/107399/2005)
- 'Structure of the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products' (EMEA/HMPC/100824/2005 Rev.2)
- 'Timetable for the establishment of a Community herbal monograph [not resulting from a referral procedure]' (EMEA/HMPC/126542/2005)
- 'Procedure for the preparation of Community monographs for herbal medicinal products with well-established medicinal use' (EMEA/HMPC/182352/2005 Rev.2)

- ‘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 herbal monograph = document whose purpose is to provide a scientific summary of all data available on the safety and efficacy of a herbal substance/preparation¹ intended for medicinal use.

Abbreviations

CHMP – Committee for Medicinal Products for Human Use

CPMP – Committee for Proprietary Medicinal Products

EMA – 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)
- ‘Guideline² 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)

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

² 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 electronic file (specific "Community monographs" folder in "HMPC" folder). Rapporteur/CoRapporteur shall provide copies of relevant documents to the HMPC Secretariat.

8. Instructions

Transfer relevant information from the assessment report into the template for Community herbal monograph under the respective headings.

When information is available, it must be recorded in accordance with the 'Guideline on Summary of Product Characteristics'.

For the title of the Community herbal monograph 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 monograph on Hawthorn Leaf and Flower will be:

Community herbal monograph 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

For the keywords section of the monograph, 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 Community monographs for traditional herbal medicinal products

1. NAME OF THE MEDICINAL PRODUCT

The following standard statement should be included:

[To be specified for the individual finished product.]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The qualitative and quantitative declaration should be given in accordance with relevant herbal quality guidance, in particular the 'Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00 Rev.1 and EMEA/CVMP/814/00 Rev.1) and the '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).

Two footnotes shall appear in the title of the section.

The first footnote concerns the material's compliance to monograph(s) of the European Pharmacopoeia that provide definitions of the herbal substance/herbal preparation(s), or, in its(their) absence, compliance with monograph(s) of an official pharmacopoeia of a Member State if available. If such monograph(s) does(do) not exist, the definition of the herbal substance/herbal preparation(s) must be added as far as possible in analogy to the Ph. Eur. as footnotes per substance and preparation.

The following standard text for the first footnote can be used:

<The material complies with the Ph. Eur. <monograph><monographs>.>

The second footnote is a standard statement:

[The declaration of the active substance(s) for an individual finished product should be in accordance with relevant herbal quality guidance.]

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).

i) Herbal substance

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

ii) Herbal preparations

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)

3. PHARMACEUTICAL FORM

Describe the type of dosage forms relevant for the herbal substance and/or herbal preparation(s) and intended route of administration.

For example: 'Herbal substance or herbal preparations in solid or liquid dosage forms for oral use'.

The following standard statement should be included:

[The pharmaceutical form should be described by the European Pharmacopoeia full standard term.]

Note that only oral, external and/or inhalation preparations 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).

4. CLINICAL PARTICULARS³

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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, children⁴, adolescents⁵, adults, elderly:
 - a) Specific dose
 - b) Maximum recommended single, daily and/or total dose, and
 - c) Dosage frequency
- 2) 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.
- 3) Duration of use and any restriction on duration of use, if relevant.
- 4) Intake of the product in relation to food intake.
- 5) Method of administration and/or relevant instruction for correct administration/use.
- 6) 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.>

³ For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.

⁴ Between 2 and 11 years of age

⁵ Between 12 and 18 years of age

4.3 Contraindications

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

- i) Contraindications including specific patient populations.
- ii) Other medicines or classes of medicines, which should be specifically avoided (i.e. contraindicated), if applicable a cross-reference to section 4.5 should be given. In general, patient populations not studied should be mentioned in section 4.4 unless a safety issue can be predicted.
- iii) Only if pregnancy is strictly contraindicated, should it be mentioned here. In section 4.6, 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)>.

4.4 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.

- 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.

Note that contraindications should be mentioned under section 4.3 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.

4.5 Interaction with other medicinal products and other forms of interaction

This section should provide information on the potential for clinically relevant interactions based on the pharmacological properties of the medicinal product.

- i) 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)

4.6 Pregnancy and lactation

- i) For examples of pregnancy and lactation statements, see⁶ 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 statement can be used:

<In the absence of sufficient data, the use during pregnancy and lactation is not recommended.>

4.7 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.

4.8 Undesirable effects

This section should provide comprehensive information based on all adverse reactions (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' ($\geq 1/10$) to 'not known' (cannot be estimated from the available data).

If there is no information on adverse reactions, the following statement should be included:

⁶ Also published in the appendix 1 of the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling' (EMA/CHMP/203927/2005)

<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.>

4.9 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.>

5. PHARMACOLOGICAL PROPERTIES⁷

Note that the information on pharmacological properties of traditional herbal medicinal products is not required, unless such data are relevant for the safe use of the product.

Where relevant, the following standard statement should appear in section 5.3 Preclinical safety data:

<Tests on <reproductive toxicity,><genotoxicity,><and><carcinogenicity> have not been performed.>

6. PHARMACEUTICAL PARTICULARS

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.>

7. DATE OF COMPILATION/LAST REVISION

⁷ For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.