EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 March 2024
EMA/HMPC/418902/2005 Rev. 6
Committee on Herbal Medicinal Products (HMPC)

Template for Assessment report for the development of European Union herbal monographs and European Union list entries

Draft – Revision 6

Adoption by Committee on Herbal Medicinal Products (HMPC)	11 January 2007
Revision 1 adopted by HMPC	6 November 2008
Revision 2 adopted by HMPC	6 May 2010
Revision 3[1] adopted by HMPC	10 May 2011
Revision 4 adopted by HMPC	25 March 2014
Revision 5 agreed by HMPC Organisational Matters Drafting Group (ORGAM DG)	May 2014 September 2014
Coordination with HMPC Working Party on European Union Monographs and European Union List (MLWP)	July2014
Revision 5[2] adopted by HMPC	29 September 2014
Draft Revision 6 adopted by HMPC for release for consultation	20 March 2024
Start of public consultation	15 April 2024
End of consultation (deadline for comments)	15 July 2024

Comments should be provided using this template. The completed comments form should be sent to hmpc.secretariat@ema.europa.eu

Keywords	Committee on Herbal Medicinal Products; HMPC; European Union herbal monographs; European Union list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products; herbal medicinal products; traditional herbal medicinal products; traditional use; well-established medicinal use; benefit-risk assessment; assessment report

[1] Changes introduced in section 6 Overall conclusions.
[2] Corrected reference to legislation: e.g. 'Directive 2001/83/EC as amended' replaced with 'Directive 2001/83/EC'.

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<date>
<doc ref>
Committee on Herbal Medicinal Products (HMPC)

Assessment report on <plant, plant part>

Insert botanical name of the plant according to the binomial system (genus, species, variety and author), [comma] the plant part in Latin.

<Draft><Final>

<Based on Article 10a of Directive 2001/83/EC (well-established use)>

<Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)>

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<Rapporteur to include text> *Copy from monograph section 2i).*
Herbal preparation(s)	<Rapporteur to include text> *Copy from monograph section 2ii).*
Rapporteur(s)	<Rapporteur to include text> *Name of HMPC member (not Member State). If not the same rapporteur since last version, all rapporteurs should be listed and the version specified in brackets.*
Assessor(s)	<Rapporteur to include text> *Name of assessor(s) should only be included if different from rapporteur. If not the same assessor(s) since last version, all assessors should be listed and the version specified in brackets. The assessor's area of expertise should also be specified e.g. quality, non-clinical or clinical assessor.*
Peer-reviewer	<Rapporteur to include text> *If not the same peer-reviewer since last version, all peer-reviewers should be listed, and the version specified in brackets.*

<Note: This draft assessment report is published to support the public consultation of the draft <European Union herbal monograph> <public statement> on <plant, plant part>. It is a working document, not yet edited, and shall be further developed after the release for consultation of the <monograph> <public statement>. Interested parties are welcome to submit comments to the HMPC

secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft <monograph> <public statement>.>

Note:

- *All instruction notes (in green) must be deleted before finalising the AR.*
- *None of the headings should be deleted during the preparation of the AR. If there is no information available for a heading, please insert 'No information available'. If a heading is not relevant, please insert 'Not applicable'. There are several examples of standard sentence to be used, if appropriate.*
- *Text should be written in the provided text boxes <Rapporteur to include text> only. Do not change the prespecified font of the text field. Suggested font: Verdana 9.*
- *Critical assessment (e.g. comments on the validity and interpretation of the data, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter, in italic in a box. The principle of the template is to make clear distinctions between presentation of data (methodology and results) and the assessment of the data ("assessor's comment"). In case a sentence is concluding something which is not a comment from the assessor i.e. likely from an article but it seems it is concluded by the rapporteur; 'According to the author' to be added. Chapters with a heading including the word 'conclusion' should include a summary of all critical assessment of the assessor for that particular chapter. If an assessor's comment is not needed, the Rapporteur should delete the box inserted in the template. If an additional assessor's comment is needed, the Rapporteur should include as appropriate.*
- *The report should be sufficiently detailed to allow for secondary assessment of the available data by other HMPC experts.*
- *All tables to be numbered in sequential order. The tables in the template should all be filled by the rapporteur unless there is no data available. In these exceptional cases, the table should be deleted and replaced with 'No information available'.*
- *All sections of the monograph should have a justification in the AR.*
- *In addition to guidance documents established by HMPC (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/herbal-medicinal-products-scientific-guidelines), the rapporteur, assessor(s) and peer-reviewer should also pay attention to other EMA/ICH/EC guidance documents of relevance for the development of monographs for example the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling' (EMEA/CHMP/203927/2005) and 'A guideline on summary of product characteristics (SmPC)' September 2009 Revision 2.*

Table of contents

1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

<Rapporteur to include text>

Insert only reference to the relevant European Pharmacopoeia monograph or in absence thereof, to the monograph of a national pharmacopoeia or national codex currently used officially in a Member State. In their absence, state that no official quality standard available. Reference to other bibliographic sources is possible.

- Herbal preparation(s)

<Rapporteur to include text>

Insert only reference to the relevant European Pharmacopoeia monograph or in absence thereof, to the monograph of a national pharmacopoeia or national codex currently used officially in a Member State. In their absence, state that no official quality standard available. Reference to other bibliographic sources is possible. This sections is related to available quality standards and there is no need to repeat information on all preparations included in the monograph.

- Relevant constituents for this assessment report

<Rapporteur to include text>

Include a very short overview on relevant constituents, no detailed figures or structures.

1.2. Search and assessment methodology

The Rapporteur shall undertake a comprehensive search of relevant scientific literature and articles, Acts of law and regulations and other relevant sources. The rapporteur should carefully select the references considered to be relevant. Cross-reference to the list of references in Annex, which should list separately the references supporting the assessment report.

Examples of scientific databases to be searched are Medline, PubMed, Cochrane Database of Systematic Reviews, EMBASE etc. The Rapporteur shall describe the searches with database assessed, key words, date, and filters used, if applicable e.g. restrictions with regard to language and date of publication. The Rapporteur shall describe the advanced search methodology/strategy, key words, scheme, use of additional tools (e.g. MeSH). Importantly, the Rapporteur should present the plant names used in the searches including the scientific plant name(s).

Additional relevant references could also be retrieved from the checked references. Examples of books are Hagers Handbuch, The Complete German Commission E Monographs, PDR for herbal medicines etc.

The Rapporteur should also take into consideration information provided by the Member States relating to safety/pharmacovigilance included in the market overview provided by the Member States.

The Rapporteur shall also search for data, including alerts, from EU regulatory authorities. In addition, information from non-EU regulatory authorities for examples Health Canada monographs or WHO monographs could be searched, if relevant to herbal substances and preparations in EU.

The rapporteur in collaboration with pharmacovigilance colleagues, should check data from the EudraVigilance database. If relevant, other pharmacovigilance databases could be searched e.g. VigiBase.

The rapporteur should check the EURD-list if a PSUSA-procedure(s) has been finalised. If so, the rapporteur should liaise with Lead Member State (LMS) for the outcome of the PSUSA.

The rapporteur should also check consistency with other monographs within the therapeutic area. However, the rapporteur should be careful to avoid transferring the conclusions or indications, which were based on specific data and assessment from one monograph to another.

Scientific databases

- ☐ Scientific/Medical/Toxicological databases

  <Rapporteur to include the name of database, the period covered, search date, search terms, and if appplicable the filters used>
- ☐ Pharmacovigilance databases
  - ☐ data from EudraVigilance
  - ☐ from other sources (e.g. data from VigiBase)
- ☐ Other <Rapporteur to include text>

Books

- ☐ <Rapporteur to include text>

Regulatory practice

- ☐ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)
- ☐ Market overview (including pharmacovigilance actions taken in member states)
- ☐ PSUSA
- ☐ Feedback from experiences with the monograph during MRP/DCP procedures
- ☐ Ph. Eur. monograph
- ☐ Other <Rapporteur to include text i.e referral, data submitted by the IP>

Consistency (e.g. scientific decisions taken by HMPC)

- ☐ Public statements or other decisions taken by HMPC
- ☐ Consistency with other monographs within the therapeutic area
- ☐ Other <Rapporteur to include text>

Other

☐ <Rapporteur to include text>

1.3. <Main changes introduced in the <Number as appropriate> revision>

<Rapporteur to include text, if applicable>

During a revision the rapporteur should carefully select the references considered to be relevant to keep the assessment report concise. The rapporteur may also delete or shorten the text included in the first/previous version, as considered appropriate.

When the assessment report is revised, the rapporteur should briefly summarise the main changes under this section. In particular, changes that support relevant changes in the monograph should be summarised in this section. This section should be short and refer to the chapters that have been changed.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

According to the information provided by the National Competent Authorities. Data are collected using the template entitled 'Document for information exchange for the preparation of the assessment report for the development of European Union monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list' (EMEA/HMPC/137093/2006).

The information on the regulatory status of the products may preferably include the nature of the authorisation granted for the product to access the market (MA based on full or mixed application, MA based on bibliographic application as per Article 10a of Directive 2001/83/EC, traditional use registration, etc.) to establish the period of medicinal use:

- for TU: at least 30 years of medicinal use including at least 15 years in the EU
- for WEU: at least 10 years of approved medicinal product in the EU.

Information on medicinal products marketed in the EU/EEA

Table <*insert number*>. Overview of data obtained from marketed medicinal products.

Herbal substance/ preparation	**Indication**	**Posology and method of administration** *Posology, age groups, pharmaceutical form, method of administration, duration of use*	**Regulatory Status** *Type of Marketing authorisation/registration where possible, date, Member State*
As reported in the market overview	*As reported in the market overview*	*As reported in the market overview.*	*Brand names can be kept during discussion but shall be deleted at publication stage*

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

<Rapporteur to include text or insert 'Not applicable'>

Include any other information on combination medicinal products considered relevant for the establishment of the monograph. For combination monographs the table above should be deleted.

Table <*insert number*>. Information on relevant combination medicinal products marketed in the EU/EEA.

Herbal substances/ preparations	**Medicinal use**	**Posology and method of administration** *Posology, age groups, pharmaceutical form, method of administration, duration of use*	**Regulatory Status** *Type of Marketing authorisation/registration where possible, date, Member State*
As reported in the market overview	*As reported in the market overview*	*As reported in the market overview.*	*Brand names can be kept during discussion but shall be deleted at publication stage*

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on other products marketed in the EU/EEA (where relevant)

<Rapporteur to include text or insert 'Not applicable'>

Include any other relevant information on products available on the market which are neither authorised nor registered (e.g. medical devices, food supplements, cosmetics).

The information can be provided using the same format (table) as for the information on medicinal products. Only products that have sufficient information on preparation, medicinal use and posology should be included in the table below.

Table <*insert number*>. Information on other products marketed in the EU/EEA.

Herbal substance/ preparation	**Medicinal use**	**Posology and method of administration**	**Regulatory Status** *Food supplement/ Medical device/Cosmetic, date, Member State, date, if available*
As reported in the market overview	*As reported in the market overview*	*As reported in the market overview.*	*Brand names can be kept during discussion but shall be deleted at publication stage*

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

2.1.2. Information on products on the market outside the EU/EEA

<Rapporteur to include text or insert 'Not applicable'>

Include information on products marketed outside the EU/EEA if available (data from literature to be reported only in section 2.2).

The information can be provided using the same format (table) as for the information on medicinal products marketed in the EU. Only products that have sufficient information on preparation, medicinal use and posology should be included in the table below. Brand names can be kept during discussion but shall be deleted at publication stage.

Table <*insert number*>. Overview of information on products on the market outside the EU/EEA.

Herbal substance/ preparation	**Indication/Medicinal use**	**Posology and method of administration** *Posology, age groups, pharmaceutical form, method of administration, duration of use*	**Regulatory Status** *Type of regulatory status where possible, date, Country*

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

2.2. Information on documented medicinal use and historical data from literature

<Rapporteur to include text>

For each herbal substance/preparation, provide evidence of history and extent of use, obtained from literature, and preferably classified whether predominantly European or non-European tradition, and the current use. Only relevant data that will be used for conclusion on traditional use should be included.

For each herbal preparation, provide information on traditional/current indication(s), specified strength and posology, route of administration, duration of use per indication. Evaluation on the use should be presented both on the known use(s) in the EU, and, if applicable, use(s) outside the EU. Only substances/preparations that have sufficient information on preparation, medicinal use and posology should be included in the table below.

Table <*insert number*>. Overview of historical data.

Herbal substance/ preparation	**Documented use / Traditional use**	**Posology and method of administration** *Posology, age groups, pharmaceutical form (if available), method of administration, duration of use*	**Reference and date of the reference**

Herbal substance/ preparation	Documented use / Traditional use	Posology and method of administration *Posology, age groups, pharmaceutical form (if available), method of administration, duration of use*	Reference and date of the reference

2.3. Overall conclusions on medicinal use

For each herbal substance(s)/preparation(s) with complete information, provide an overview of the available sources (market data and/or literature) that provide evidence of:
- period of use

- for TU: at least 30 years of medicinal use including at least 15 years in the EU
- for WEU: at least 10 years of approved medicinal product in the EU.

- specified strength and specified posology
- indications suitable to the legal requirements in the relevant route of administration.

In the table on 'Overview of evidence on period of medicinal use', the same information as specified in the tables in section 2.1 and 2.2 should be included, without modifications.

Table <*insert number*>. Overview of evidence on period of medicinal use.

Herbal substance/ preparation	Indication	Posology and method of administration *Posology, age groups, duration of use, method of administration*	Period of medicinal use *The date of the reference should be used.*

<Clinical efficacy and safety based on Article 10a of Directive 2001/83/EC (well-established use), is evaluated in chapter 4 'Clinical data' and chapter 5 'Clinical Safety/Pharmacovigilance'. The non-clinical safety is evaluated in chapter 3 'Non-clinical data'.>

<Clinical safety for preparations that fulfil the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use based on Article 16d(1), Article 16f and Article 16h of of Directive 2001/83/EC is further evaluated in chapter 5 'Clinical Safety/Pharmacovigilance'. The non-clinical safety is evaluated in chapter 3 'Non-clinical data'.>

<Rapporteur to include text>

The Rapporteur should discuss all available sources showing that the requirements for the period of medicinal use are fulfilled and the indication and posology that will be considered for inclusion in the monograph to be further evaluated in chapter 3-5. For example, the choice for the wording of traditional use indications vis-à-vis existing wordings in monographs in the same therapeutic area should be briefly discussed/justified. Information on duration of use should also be discussed.

3. Non-Clinical Data

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 (if such information are not known from the reference, this should be stated as well). The studies should be organised in studies performed with preparations covered by the monograph (or similar preparations), other preparations (different to those covered by the monograph) and single (isolated) substances), if the single (isolated) substance is relevant for therapeutic indication or safety of the herbal substance(s)/preparation(s) in the monograph.

The rapporteur should separate in vitro data from in vivo data, preferably as a new heading in italic (but not with a numbering).

For all studies cited, it should be stated clearly, which concentrations/dosage have been used and in which concentrations/ dosages effects were seen; it should be stated if e.g. a IC_{50} or EC_{50} was calculated.

The Rapporteur should discuss the relevance of the findings in relation to the herbal preparations accepted in the monograph. A comparison to a human equivalent exposure should be given, if considered relevant, using allometric factors according to the "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/07 Rev. 1).

The rapporteur should discuss whether findings have implications for human safety and whether additional data in human is needed to assess this (e.g. there are findings regarding carcinogenicity, but receptors are different between target species and man).

Critical assessment (e.g. comments on the validity and interpretation of the data, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter and should include findings that need to be reflected in the monograph.

See also 'Non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products' (EMEA/HMPC/32116/2005) and other relevant EMA non-clinical scientific guidelines for more details.

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

<Rapporteur to include text>

The Rapporteur shall describe pharmacological data that support the indication(s) in the monograph. The rapporteur should carefully select the main studies to be included in the table below i.e. studies with relevant model/animal species and dosage for humans.

Preferably, references cited should be summarised in text in the style of an abstract and details presented in a table (see table template below for further information). For each therapeutic area, studies of relevance for potential WEU and/or TU indication(s) should be included in a separate table. Only studies with all information available to complete all columns in the table should be included in the table. Importantly, the reference should be presented sufficiently detailed to allow for secondary assessment of the available data by other HMPC experts. In-vitro studies should only be given in the table in exceptional cases since missing PK data will not allow to discuss the relevance for clinical use.

The rapporteur should consider for each study: objective, design, duration, dose, endpoints, positive and negative controls, statistical method. If such information is not given in the reference, this should be stated as well. The Rapporteur should assess:

- *Is the design of the studies adequate?*
- *Is the posology/concentration (in-vitro/ex-vivo) at least in a biological imaginable order of magnitude (e.g. in vitro IC50<100 µg/ml for extracts)*
- *Is the choice of endpoints/controls and methods of assessment as well as the duration of the study in accordance with scientific guidelines.*
- *Magnitude and relevance of the effect.*

All the studies included in this chapter should be assessed, and a clear statement should be given on the relevance of the model and dosage for humans.

Table <*insert number*>. Overview of the main non-clinical data.

Herbal preparation tested	**Concentration/ Dosage** *Route of administration for in vivo studies*	**Animal species/ Experimental model** *In vivo/ In vitro*	**Reference** *Author(s) and year of publication*	**Main outcome(s) according to the authors** *Main outcome/ result of the study according to the authors*
comparable/similar preparations to preparations of the monograph				
other preparations				
single substances				

Assessor's comment:

<Rapporteur to include text>

For WEU monographs, discuss the possible mechanism of action and/or a statement that the mechanism of action is not known.

3.1.2. Secondary pharmacodynamics

<Rapporteur to include text>

The Rapporteur shall briefly describe the results from studies which are not connected to the indication(s) agreed in the monograph. The main focus should be from a safety perspective and in vitro results is considered not relevant for the establishment of a monograph. If a recent review of good quality is available, this reference could be preferable to keep this section short and concise.

Assessor's comment:

<Rapporteur to include text>

3.1.3. Safety pharmacology

<Rapporteur to include text>

The following points should be addressed if data is available:

- *Cardiovascular system (including QT prolongation in-vitro/in-vivo)*
- *Central nervous system*
- *Respiratory system*
- *Other e.g. Renal and GI system*

Assessor's comment:

<Rapporteur to include text>

3.1.4. Pharmacodynamic interactions

<Rapporteur to include text>

Potential pharmacodynamic drug interactions may include:

- *Interactions at receptor level*
- *Possible co-medications in the clinical setting*
- *Alerts from safety pharmacology or toxicology studies*

Assessor's comment:

<Rapporteur to include text>

3.1.5. Conclusions

<Rapporteur to include text>

<Results from relevant non-clinical pharmacology studies on <*insert*> are limited and not required.>

The conclusions shall include statements on the presence and usefulness of the data. The Rapporteur should discuss the relevance of the findings in relation to the herbal substances/preparations accepted in the monograph, especially as regards to the posology used in the animal testing in comparison to the therapeutic posology in humans.

If considered relevant, safety pharmacology findings predicting potential adverse events in humans should be discussed.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

<Rapporteur to include text>

If possible, the Rapporteur to differentiate between Absorption, Distribution, Metabolism, Elimination and Pharmacokinetic interactions with other medicinal products. The rapporteur should separate in vitro data from in vivo data, preferably as a new heading in italic (but not with a numbering). 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 (if such information are not known from the reference, this should be stated as well). The studies should be organised in studies performed with preparations covered by the monograph (or similar preparations), other preparations (different to those covered by the monograph) and single (isolated) substances).

Assessor's comment:

<Rapporteur to include text>

<Specific data on pharmacokinetics and interactions are not available.>

The Rapporteur shall include statements on the presence and usefulness of the data. Comment on the relevance of the animal species used for human safety assessment e.g. considering metabolic

patterns. Other important aspects may include major differences in absorption/bioavailability, interindividual/interspecies variability, elimination rates (differences in t½), etc.

Comment on other issues that may be of importance for the safety assessment e.g. distribution to target organs, excretion routes, and pharmacologically active metabolites. Discuss interspecies differences and compare with the clinical situation.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

<Rapporteur to include text>

The single-dose data should be very briefly summarised, in order by species, by route.

Assessor's comment:

<Rapporteur to include text>

To be considered:

- *The duration of observation (14 days in a standard GLP study) and a short statement on whether studies revealed low or high acute toxicity should be included.*
- *It is considered useful to include the approximate lethal dose or observed maximum non-lethal dose.*
- *The clinical signs of acute toxicity (briefly) and the mode and time of death (early/same day or delayed).*
- *Specify target organs, (histo)pathology if available.*

3.3.2. Repeat dose toxicity

<Rapporteur to include text>

The studies should be organised by herbal substance/preparation, species and route of administration. A short description of the design (strain, route of administration, dose groups, number animals/gender/group, recovery groups if any, toxicokinetics if performed).

The main findings should be comprehensively described, namely: death, body weight, relevant laboratory findings, target organs with type of histopathological lesions, dose-dependency, onset, severity, species or gender related differences and duration of toxic effect.

The No Observed Adverse Effect Level (NOAEL) in the different species should be provided (if established) with comments on the relation of

the systemic exposure at that dose level to the systemic exposure in humans given the maximum intended dose (exposure margin).

A statement whether reversibility has been demonstrated in the recovery group should be included.

Table <*insert number*>. Overview of repeat dose toxicity studies.

Study (reference)	Herbal substance/ preparation/ isolated compounds	Species/Sex/ Number/ Group	Dose/Route/ Duration	NOEL/NOAEL (mg/kg/day) according to the authors	Major findings according to the authors

Assessor's comment:

<Rapporteur to include text>

Highlight the important findings; discuss the mechanistic background and the margin to the clinical exposure. Discuss if the studies fulfil the current guideline requirements.

3.3.3. Genotoxicity

<Rapporteur to include text>

Sort the performed tests according to the 'level' of genotoxicity, i.e. mutagenicity (gene mutations), chromosomal aberrations (clastogenicity) in-vitro, chromosomal aberrations (clastogenicity) in- vivo, primary DNA damage and other genotoxic effects. Preferably, present results in a table (see example below). See also 'Assessment of genotoxicity of herbal substances/preparations' (EMEA/HMPC/107079/2007).

Table <*insert number*>. Overview of genotoxicity studies.

Type of test/reference	Test system	Herbal substance/ preparation/ isolated compound	Concentrations/ Concentration range/ Metabolising system	Results positive/negative/ equivocal
Gene mutations in bacteria	*Salmonella strains*		*+/- S9*	
Gene mutations in mammalian cells	*CHO-cells, HGPRT-locus*		*+/- S9*	

Chromosomal aberrations in vivo	*Mouse, micronuclei in bone marrow*		*+/- S9*	

Assessor's comment:

<Rapporteur to include text>

Issues to consider when evaluating genotoxicity tests:

For in-vitro tests:
- *Which strains /cells are used and which endpoints.*
- *Selection of concentrations.*
- *Stability in the medium (check of concentration/degradation products).*
- *Metabolising system.*
- *Positive and negative controls.*
- *Treatment time/sampling time.*
- *Criteria for positive response as/if given by the authors.*
- *Concentration-response relationship.*
- *Reproducibility.*
- *Cytotoxicity / cell survival.*

For in-vivo tests:
- *Which species/strain/model was used?*
- *Number and gender of animals.*
- *Doses and exposure established by toxicity or kinetics.*
- *Metabolic differences between species and human.*
- *Treatment and sampling times.*
- *Criteria in the study for positive response.*
- *Dose/time-response relationship.*

Issues to discuss:
- *Positive findings in either in-vitro or in-vivo tests.*
- *Mechanistic background: mutagenic or clastogenic.*
- *Is a threshold approach possible?*
- *If yes, what is the margin of safety with human plasma level/exposure?*
- *Discuss if the studies fulfil the current guideline requirements.*
- *Justification(s) for monograph section 5.3.*

3.3.4. Carcinogenicity

<Rapporteur to include text>

Give a short summary of results including neoplastic changes as well as relevant non-neoplastic changes, as appropriate. Non-neoplastic changes should be discussed with reference to the observations in repeat-dose toxicity studies. Preferably, list results in a Table (example below).

Table <*insert number*>. Overview of carcinogenicity studies.

Study (reference)	Herbal substance/ preparation/ isolated compound	Dose/Route	Species/No. of animals	Major findings

Assessor's comment:

<Rapporteur to include text>

Issues to be considered in detail:

- *Species strain and gender.*
- *Number of groups (control groups).*
- *Number of animals per group.*
- *Route of administration*
- *Duration of treatment.*
- *Growth (BW gain and FC)*
- *Survival at the end of the study.*
- *Tumour findings organs, type (B or Malignant), incidence.*
- *Pre-neoplastic findings.*
- *Nomenclature of tumours.*
- *Statistical methods used.*
- *Toxic findings not seen in the studies of shorter duration.*
- *Discuss if the studies fulfil the current guideline requirements.*
- *Provide suggestions and justifications for monograph section 5.3.*

3.3.5. Reproductive and developmental toxicity

<Rapporteur to include text>

Give a summary presentation of the performed studies, preferably in a table (example below) including dose-finding studies, as appropriate.

Consider information relevant to reproduction toxicity also from other studies. For instance, histopathology of reproductive organs from repeat-dose toxicity, endocrine effects etc.

Table <*insert number*>. Overview of reproductive and developmental toxicity studies.

Study	Species; Number Female/group	Herbal preparation/ Route & dose	Dosing period	NOAEL according to the authors	Major findings according to the authors
Male fertility					
Female fertility					
Embryo-fœtal development				F0 F1	
Peri & postnatal					

Assessor's comment:

<Rapporteur to include text>

Conclusions on the reproductive toxicity:
▪Comment on the relevance of the tested systems used (e.g. species/strain) (e.g. based on comparative metabolism and kinetics, comparative pharmacodynamics).
▪Evaluate exposure and distribution data in pregnant and/or lactating animals, and in offspring (including milk excretion).
▪Include critical assessment on each specific area of the studies and provide concluding remarks considering relevant findings.
▪Consider margins of exposure and assess the clinical relevance of the findings.
▪Discuss if the studies fulfil the current guideline requirements.
▪Justification(s) for monograph section 4.6 and 5.3.

3.3.6. Local tolerance

<Rapporteur to include text>

A short comment on whether the compound showed any evidence of local irritancy at the site of administration. Sensitisation studies should be included if applicable (dermal route).

Assessor's comment:

<Rapporteur to include text>

3.3.7. Other toxicity studies

<Rapporteur to include text>

Any such studies should be noted, and findings commented upon.

Assessor's comment:

<Rapporteur to include text>

3.3.8. Conclusions on toxicological data

<Rapporteur to include text>

<Non-clinical information on the safety of <*insert*> is <missing><scarce><limited>. <With the limited data available it is difficult to draw any firm conclusions especially regarding <genotoxicity>< carcinogenicity> <and reproductive and developmental toxicity.>

<As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.>

The following text is included in the monograph section 4.6:

See decision tree in the 'Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling' (EMEA/CHMP/203927/2005).

<Overall, the toxicology programme revealed <*insert*>. This information has been included in the monograph section <*insert*>.>

The following text is included in the monograph section 5.3: <<Tests ><Adequate tests> on reproductive toxicity, genotoxicity and carcinogenicity <have not been performed>.>

In terms of structure the conclusion should follow the presentation of the results above. The rapporteur should conclude on available toxicological data and the potential relevance for the human use. Special emphasis should be put on genotoxicity, carcinogenicity and reproductive and developmental toxicity findings. In case of positive genotoxic effects, tumour findings and/or developmental/reproductive toxicity findings, the possible relevance for the human situation should be discussed and concluded upon.

If present in the herbal substance(s)/preparation(s), constituents with safety concerns (e.g. estragole, thujone etc) should also be discussed.

Justifications for monograph section 4.6 and 5.3 should be included.

3.4. Overall conclusions on non-clinical data

<Rapporteur to include text>

In this part, the most important conclusions from section 3.1.5. and 3.3.8 should be summarised.

Ensure correspondence with monograph (particularly 5.3 Non-clinical safety data and 4.6 Pregnancy and lactation, if relevant) and that all information on non-clinical data in the monograph is explicitly assessed and supported by the scientific assessment.

The Rapporteur may consider the possible inclusion of examples provided below.

The following "standard" wording could be considered:

<Results from relevant non-clinical pharmacology studies on <*insert*> are limited and not required.>

<Specific data on pharmacokinetics and interactions are not available.>

<Non-clinical information on the safety of <*insert*> is <missing><scarce><limited>. <With the limited data available it is difficult to draw any firm conclusions especially regarding <genotoxicity>< carcinogenicity> <and reproductive and developmental toxicity.> <<Tests><Adequate tests> on reproductive toxicity, genotoxicity and carcinogenicity <have not been performed>.>

<As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.>

<Overall, the toxicology programme revealed <*insert*>. This information has been included in the monograph section <*insert*>.>

4. Clinical Data

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 (if such information is not known from the reference, this should be stated as well or consider if the reference is not relevant to include).

This chapter should focus on studies of relevance for potential WEU indication(s) available in section 2.3 i.e. at least 10 years of medicinal use in the EU is a prerequisite for the establishment of a WEU monograph. However, if the rapporteur chooses to include studies on a preparation with less than 10 years of medicinal use, the rapporteur should justify why the studies are not relevant for a WEU monograph, e.g. that there is no information available that the preparation(s) have been in medicinal use for more than 10 years in EU in these indications (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States') and that these studies will not be considered for a well-establish use monograph.

<There are numerous clinical studies performed with <*insert*>. In accordance with the guideline 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products' (EMA/HMPC/104613/2005 – Rev. 1), the assessment of well-establish use should also include if the products reported in the market overview can be considered as similar to the product studied in relevant clinical studies found in the literature (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Therefore, the scope of the assessment in this section is <*insert*>. Only studies related to these indications are included below. Beside these investigations, <*insert*> have been tested for clinical efficacy for instance in <*insert*>. There is no information available that <*insert*> have been in medicinal use for more than 10 years in EU in these indications (see chapter 2.1.1. 'Information about products on the market in the EU/EEA Member States'). Thus, these studies will not be considered for a well-establish use monograph.>

See 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products'(EMA/HMPC/104613/2005) for more details. In addition, EMA scientific guidelines on how to interpret and apply the requirements for the demonstration of efficacy set out in the EU directives should be taken into consideration. EMA scientific guidelines are available on for example insomnia, irritable bowel syndrome, pain, to give assessors guidance on relevant endpoints, validated/relevant scales, recommended study duration, choice of comparator, inclusion/exclusion criteria etc.; but also general Guidelines such as ICH E5 (R1), ICH E8 (R1)or ICH E9 should be noted.

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

<Rapporteur to include text>

For example, clinical data related to information on mechanism of action, onset and/or offset of action; support for the proposed dose and dosing interval; clinically relevant pharmacodynamic interactions with other medicinal products or substances; and possible genetic differences in response.

Assessor's comment:

<Rapporteur to include text>

For WEU monographs, relevant information in accordance with the SmPC guideline to be included in the monograph section 5.1 should be discussed.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

<Rapporteur to include text>

If possible, differentiate between Absorption, Distribution, Metabolism, Elimination. Also, data on preparation and isolated compounds should be specified.

Assessor's comment:

<Rapporteur to include text>

For WEU monographs, relevant information in accordance with the SmPC guideline to be included in the monograph section 5.2 should be discussed.

4.2. Clinical efficacy

In the following sections on clinical efficacy the rapporteur should consider for each study: objective, design, duration, study participants (inclusion/exclusion criteria), sample size, dose, efficacy variables (primary and secondary endpoints), effect size, statistical method(s), numbers analysed, drop-outs. If such information is not given in the reference, this should be stated as well. The Rapporteur should assess:

Is the design of the studies adequate (randomised, active and/or placebo controlled trials) and in line with scientific guidelines?

Is the patient population appropriate?

- *Is the choice of endpoints and methods of assessment as well as the duration of the study in accordance with guidelines for the*

relevant indication (if available). Where validated scales used? Duration of the study should be clinically justified.

- *Magnitude and clinical relevance of the effect. Was there a pre-definition of clinically relevant difference?*
- *Do the results support the indication?*

All the studies should be assessed, and a clear statement should be given in an assessor's comment, if the results are sufficient to support the usage in the indication of the monograph or not.

4.2.1. Dose response studies

<Rapporteur to include text>

For all studies cited, it should be stated clearly, which concentrations/dosage have been used and in which concentrations/ dosages effects were seen.

Assessor's comment:

<Rapporteur to include text>

4.2.2. Clinical studies (case studies and clinical trials)

<Rapporteur to include text>

Preferably, references cited should be summarised in text in the style of an abstract and only specific details briefly presented in a table (see table template below for further information). For each therapeutic area, studies of relevance for potential WEU indication(s) should be included in a separate table. Only studies with all information available to complete all columns in the table should be included in the table. Importantly, the reference should be presented sufficiently detailed to allow for secondary assessment of the available data by other HMPC experts. Information on undesirable effects is to be addressed under section 5 'Clinical Safety'.

Assessor's comment:

<Rapporteur to include text>

Comment on validity of the study as well as the clinical relevance of the results. All studies cited should be followed by an assessor's comment.

Table <*insert number*>. Clinical studies on <*herbal substance/preparation*> in <*insert therapeutic area*>.

The purpose of the table is to give a quick overview and focus of the relevant studies. The table should not include full sentences or value judgments such as "small", "superior" or "significant", only numbers.

Study and study objective *Reference; Aim and objective(s) of study*	**Study design** *Study design; Type of Control; Study duration, Single centre/multi centre, Country(ies)*	**Treatment** *Herbal preparation, pharmaceutical form; Control treatment; Dosage Regimen; Route of Administration; Duration of treatment*	**Number of subjects** *Sample size separated by treatment arm(i.e. numbers analysed)*	**Type of subjects** *Age, sex, ethnicity/genetic polymorphism, healthy or Diagnosis of Patients (inclusion/exclusion criteria)*	**Endpoints** *Primary and secondary endpoints. Specify which measure/scale was used and which comparison was done (for example difference in change from baseline or ratio of responders).*	**Outcomes** *Numerical results/scores including 95% CIs (if available).*

4.3. Clinical studies in special populations (e.g. elderly and children)

<Rapporteur to include text>

In this section clinical studies in special populations (e.g. elderly and children) not included in section 4.2 should be presented. Preferably, references cited should be summarised in text in the style of an abstract and only specific details briefly presented in a table, if applicable i.e. only studies with all information available to complete all columns in the table should be included in a table. Importantly, the reference should be presented sufficiently detailed to allow for secondary assessment of the available data by other HMPC experts. Information on undesirable effects is to be addressed under section 5 'Clinical Safety'.

Assessor's comment:

<Rapporteur to include text>

4.4. Overall conclusions on clinical pharmacology and efficacy

<Rapporteur to include text>

A statement about the conclusions in terms of establishing efficacy that can be drawn from the clinical efficacy documentation should be provided here, as well as the rationale for including or excluding an indication(s), population(s) and posology/posologies.

The key findings, the strength of the evidence and uncertainties should be summarised and concluded upon. Discuss and conclude on the importance of the favourable effects observed in relation to the target disease and the target population. Discuss what magnitude of the effect can be conserved as meaningful and how do the observed effects compare to this. A clinically relevant effect is not the same as statistically significant effect and is different for different therapeutic areas. Discuss the impact of uncertainties and limitation of the data. The main clinical studies should be described with respect to randomisation, blinding, control and study size (i.e. the quality of the studies) and the robustness/limitations of the results e.g. too small sample size, representativeness of patient population, single pivotal study, or inconsistency of findings between studies. The strength of evidence for efficacy:

- Number of subjects studied

- Magnitude and consistency of effects seen

- Balance between positive and negative results.

Factors which have to be taken into account in order to establish a well-established medicinal use of active substances of medicinal products are:

- The time over which a substance has been used,

- Quantitative aspects of the use of the substance,

- The degree of scientific interest in the use of the substance (reflected in the published scientific literature) and

- The coherence of scientific assessments.

Lack of information in certain groups of patients (children, elderly, women with childbearing potential etc.) should be mentioned.

No reference to traditional use should be included in this section.

5. Clinical Safety/Pharmacovigilance

See 'Assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products'(EMA/HMPC/104613/2005) for further details. In addition, EMA scientific guidelines on how to interpret and apply the requirements for the demonstration of safety set out in the EU directives should be taken into consideration.

In case different safety profile for different preparations, populations, duration of use and/or method of administration this should be specified e.g. oral use/cutaneous use.

5.1. Overview of toxicological/safety data from market overview

<Rapporteur to include text>

Safety information from products on the market should be presented in this section.

<No data available.><The following safety information are included in the SmPC of products on the market:>

Table <*insert number*>. Safety information from products marketed in the EU/EEA.

Herbal substance/ preparation	SmPC section	Safety information	Member State

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

5.2. Patient exposure

<Rapporteur to include text>

This section should provide estimates of the size and nature of the population exposed from both clinical studies and post-marketing information, if available. This information should be presented by

formulation or route of administration. Information on patient exposure coming from:
- pre-marketing (number of patients in clinical trials, see table below)
- post-marketing (information from PSUR)

Particularly, indicate the safety database for paediatric patients by age groups or refer to section 5.5.1.

Information on the exposure related to uses under other regulatory frameworks (food/cosmetics/other products) may also be included.

Table <*insert number*>. Overview of the patient exposure.

	Patients enrolled	**Patients exposed**	**Patients exposed to the proposed dose range**	**Patients with long term* safety data**
Placebo-controlled				
Active-controlled				
Open studies				
Post marketing				

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Assessor's comment:

<Rapporteur to include text>

Discuss any limitations of the safety database in relation to the proposed target population. The Rapporteur may consider the possible inclusion of the following examples:

<No data available.>

<Aside from market presence and data from studies, there are no concrete data concerning patient exposure.>

5.3. Adverse events, serious adverse events and deaths

<Rapporteur to include text>

Adverse event(s) from e.g. published case reports, adverse events reported in clinical studies, or case reports from pharmacovigilance database assessed to be relevant to be included in the monograph (for guidance on assessment see e.g. Screening for adverse reactions in EudraVigilance EMA/849944/2016). Indicate if non-serious or serious. In the assessment of new adverse events, MedDRA terminology and classification system should be used, even if the original data source is not in accordance with the MedDRA terminology and classification system.

*Information on adverse events should usually **not** be strictly restricted to the indications in the monograph. Serious adverse events seen with other preparations and posologies than those in the monograph should be included when similarity could be expected.*

Results should be given by the System Organ Classification (SOC), preferred term (PT).

In all cases, the relationship between adverse events and reactions (causality included) and other variables should be addressed.

For example, variables may be:

- *Route of administration and product(s) formulation*
- *Duration of treatment.*
- *Dose regimen and schedule.*
- *Time to onset,*
- *Rechallenge/dechallenge,*
- *Biological plausibility (possible mechanism),*
- *Symptoms of the disease (lack of efficacy)*
- *Co-medication, i.e. alternative explanation/confounders*
- *Co-morbidity and co-medication as appropriate.*
- *Possible class effect,*
- *Number of reports and temporal association*
- *Cumulative and dose related toxicity.*

The quality of the data should be specified (e.g. cases appropriately documented with sufficient information about, e.g., suspected herbal substance/preparation (including correct plant name), event reported, demographics (age and gender), indication, outcome, concomitant medication).

Strengths:

- *Dose relationship*
- *Cases with positive dechallenge/rechallenge*
- *Plausible time to onset*
- *Biological and pharmacological plausibility (possible mechanism)*
- *Evidence from multiple sources, e.g. literature findings regarding similar case reports, pharmacoepidemiological studies or studies suggestive of a potential mechanism of action*

Weaknesses:

- *Poor data quality of case reports*
- *High number of cases with confounding factors / alternative explanations*
- *Signs of stimulated reporting e.g. increased media attention*
- *Abnormal reporting pattern*
- *Presence of other risk factors for the event: underlying disease, co-morbidities, co-medications*

<A search in the EudraVigilance database was done <*insert date*>. It resulted in <*insert number*> hits on <*insert search term(s)*>. In <*insert number*> cases the patients had

taken concomitant medicinal products or <*insert active substance*> was one of several substances in combination products. <*Insert further information if needed*.> Overall, no new safety issues could be identified from reports in the EudraVigilance database up to <*insert date*>.>

List clinical studies contributing to safety (could include studies not included in chapter 4). A short statement in the reference that no adverse events were reported with no further information (e.g. on how adverse events were monitored) is not considered sufficient for including the study in this chapter.

Table <*insert number*>. Clinical safety data from clinical trials where adverse events have been reported.

Reference *Aim and objective(s) of study; Reference*	**Study design** *Study design; Type of Control; Study duration*	**Treatment** *Herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration; Duration of treatment*	**Number of subjects**	**Type of subjects** *(including age, sex, ethnicity/genetic polymorphism), Healthy or Diagnosis of Patients (inclusion/exclusion criteria)*	**Adverse events**

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.8 using the EC guidance document 'A guideline on summary of product characteristics (SmPC)'. The SOC should be followed by the relevant PT. If available, rapporteur to specify the frequency of adverse reactions.

When adverse events are described for posologies or indications not included in the monograph, the relevance for the monograph should be discussed.

5.4. Laboratory findings

<Rapporteur to include text>

Information on laboratory findings (results of laboratory testing in blood, urine, etc., changes of blood pressure or heart rate or ECG parameters) coming from:
- pre-marketing (results of laboratory testing and changes of other parameters examined in clinical trials)
- post-marketing (information from PSUR).

Assessor's comment:

<Rapporteur to include text>

The Rapporteur may consider the possible inclusion of the following examples.

<No data available.>

<The value of <insert parameter> did not change during an <insert number>-month long study (<insert reference to publication>).>

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

<Rapporteur to include text>

Short summary of all relevant safety information both derived from non-clinical and clinical studies in order to substantiate the specific statements in the monograph. If detailed information already included in another section, please refer to this section.

Table <*insert number*>. Overview of exposure in children and adolescents.

	Patients enrolled	**Patients exposed**	**Patients exposed to the proposed dose range**	**Patients with long term* safety data**

Placebo-controlled				
Active-controlled				
Open studies				
Post marketing				

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph sections 4.2 and 4.4. All information in the monograph should be justified.

5.5.2. Contraindications

<Rapporteur to include text>

Short summary of all relevant safety information both derived from non-clinical and clinical studies in order to substantiate the specific statements in the monograph. If detailed information already included in another section, please refer to this section.

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.3. All information in the monograph should be justified and in line with 'A guideline on summary of product characteristics (SmPC)'.

5.5.3. Special warnings and precautions for use

<Rapporteur to include text>

Short summary of all relevant safety information both derived from non-clinical and clinical studies in order to substantiate the specific statements in the monograph. (e.g. gender related differences, effect anticipated or observed elderly, etc.). If detailed information already included in another section, please refer to this section.

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.4. All information in the monograph should be justified and in line with 'A guideline on summary of product characteristics (SmPC)'.

5.5.4. Drug interactions and other forms of interaction

<Rapporteur to include text>

Short summary of all relevant safety information both derived from non-clinical and clinical studies in order to substantiate the specific statements in the monograph. If detailed information already included in another section, please refer to this section.

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.5. All information in the monograph should be justified and in line with 'A guideline on summary of product characteristics (SmPC)'.

Cross-reference should be made to sections 3.1.4, 3.2 and 4.1.2 in this assessment report. However, an interaction supported with sufficient scientific data but not with sufficient evidence that it will cause an effect on the efficacy or safety of the preparation in humans could be relevant for monograph section 4.5 on a case-by-case basis.

5.5.5. Fertility, pregnancy and lactation

<Rapporteur to include text>

Short summary of all relevant safety information both derived from non-clinical and clinical studies in order to substantiate the specific statements in the monograph. If detailed information already included in another section, please refer to this section.

Table <*insert number*>. Overview of exposure in pregnant and lactating women.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled				
Active -controlled				
Open studies				
Post marketing				

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.6. All information in the monograph should be justified and in line with 'A guideline on summary of product characteristics (SmPC)'.

5.5.6. Overdose

<Rapporteur to include text>

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.9. All information in the monograph should be justified and in line with 'A guideline on summary of product characteristics (SmPC)'.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

<Rapporteur to include text>

Assessor's comment:

<Rapporteur to include text>

Conclude on monograph section 4.7. All information in the monograph should be justified and in line with 'A guideline on summary of product characteristics (SmPC)'.

The conclusion should be based on the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines.

5.5.8. Safety in other special situations

<Rapporteur to include text or insert 'Not available'>

Rapporteur to include data of relevance for dosage adjustments or other posology related information in specific patient groups if available, e.g. elderly population; renal impairment; hepatic impairment, patients with a particular genotype; or other relevant special population.

Assessor's comment:

<Rapporteur to include text>

Dosage adjustments or other posology related information in specific patient groups to be included in monograph section 4.2 should be stated if available. 'No information available' in specific patient groups should not be included in the monograph section 4.2.

5.6. Overall conclusions on clinical safety

<Rapporteur to include text>

In terms of structure, the conclusion should follow the presentation of the results above. Include key findings (or uncertainties) that should be part of the risk assessment. A statement about the conclusions that can be drawn from the clinical safety documentation should be provided

here (e.g., most frequent adverse reactions and other significant safety issues). For example:

- *Discuss any limitations of the safety database in relation to the proposed target population.*
- *Recall concerns identified in non-clinical studies with potential for human use.*
- *How are the findings (or lack of information) reflected in the monograph? Discuss actions needed to address important findings or limitations in the monograph (e.g. contraindications, warnings, restriction of indication). Ensure correspondence with monograph sections 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, as appropriate) and that all information in the monograph is explicitly assessed and supported by the scientific assessment.*
- *Describe relevant safety aspects specific for the paediatric population by age group where appropriate. Ensure correspondence with the recommendations in the monograph.*

In case different safety profile for different preparations or populations and/or duration of use this should be specified e.g. oral use/cutaneous use.

6. Overall conclusions

<Rapporteur to include text>

Describe key aspects only briefly, these will already have been described in detail in the respective sections. This section should cover all recommended 'well-established use' and 'traditional use' indications and conclusions shall be provided for each therapeutic indication and each herbal preparation. Importantly, the main conclusions from section 2.3, 3.4, 4.4 and 5.6 should be summarised. Statement on the presence of constituents with safety concerns (such as estragole) should be given. Ensure correspondence with the recommendations in the monograph.

Well established use monograph

The clinical studies supporting well-established use should be specified for each therapeutic indication and each herbal preparation.

If well-established use was not accepted, the reasons should be stated.

The conclusion should justify whether all the requirements for WEU (period of medicinal use, acceptable level of safety, recognised efficacy, quantitative aspects of the use of the substance and the degree of scientific interest in its use) are met or what important data is missing.

The following proposals on the final conclusion should be considered and finalised in the end of this section:

<The requirements for well-established use according to Article 10a of Directive 2001/83/EC are considered <not> fulfilled.> < The available safety and efficacy data <do not> support an use of the <herbal substance><and><herbal preparation(s)> in accordance with the conditions of use as specified in the European Union herbal monograph:>

Herbal substance/ preparation	**Indication**	**ATC code**	**Posology and method of administration**	**Duration of use**
As to be presented in a monograph	*As to be presented in a monograph*	*As to be presented in a monograph*	*As to be presented in a monograph*	*As to be presented in a monograph*

Insert the chosen proposed ATC code for each WEU indication.

Insert a summary that correspond to the recommendations in the monograph, especially safety concerns should be clearly presented in the conclusion. In particular, the specified conditions of use, including special warnings and/or contraindications should be summarised.

Traditional use monograph

The conclusion should justify whether all the requirements for TU (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, and safety) are met. The choice for the wording of traditional use indications vis-à-vis existing wordings in monographs in the same therapeutic area should be briefly discussed/justified. See also 'Public statement on the interpretation of therapeutic indications appropriate to traditional herbal medicinal products in Community herbal monographs' (EMA/HMPC/473587/2011)

A specific conclusion should be presented on the risks in the specified conditions of use, including special warnings and/or contraindications.

The following proposals on the final conclusion should be considered and finalised in the end of this section:

<The requirements for traditional medicinal use according to Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC are considered <not> fulfilled.> <It has been demonstrated that <*insert*> have been in traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, with an acceptable level of safety for:>

Herbal substance/preparation	Indication	Therapeutic area for browse search	Posology and method of administration	Duration of use
As to be presented in a monograph	*As to be presented in a monograph*		*As to be presented in a monograph*	*As to be presented in a monograph*

Insert the chosen therapeutic area for browse search for each TU indication (see browser on the EMA web for available therapeutic areas and the Matching patients friendly therapeutic areas for browse search on herbal medicines for human use with ATC therapeutic groups (level 2) (EMA/568320/2009)).

Insert a summary that correspond to the recommendations in the monograph, especially safety concerns should be clearly presented in the conclusion. In particular, the specified conditions of use, including special warnings and/or contraindications should be summarised.

List entry

The conclusions should include a statement pointing to the possibility/non-possibility to support a European Union list entry.

The Rapporteur may consider the possible inclusion of the following examples when a list entry is supported.

<The data on safety are considered sufficient to support a European Union list entry for the <above mentioned> <following> herbal preparations and indications.>

<A European Union list entry for <*insert text*> is supported only for <adolescents over 12 years,><adults and elderly>, considering the small amount of <*insert name of constituent(s)/preparation(s) with safety concerns*> in <*insert herbal preparation*> prepared from <*insert herbal substance*>.>

<A European Union list entry for <*insert text*> is supported only in <insert indication>, considering the <small><negligible> amount of <*insert name of constituent(s)/preparation(s) with safety concerns*><compared to the background exposure due to <food intake> <or> <and> <cosmetic use>> when <administered><taken>< used> at the specified posology.>

The Rapporteur may consider the possible inclusion of the following examples when a list entry is not supported.

<A European Union list entry is not supported due to lack of <adequate> data on genotoxicity.>

<Tests on genotoxicity have been performed <with <*insert herbal substance/preparation*>> <and><or><with the isolated <substance><substances> <*insert name(s)*>> only; these data cannot be extrapolated to <*insert herbal*

substance/preparation>. Therefore a European Union list entry cannot be supported due to lack of adequate data.>

<Annex><Annexes>

List of references

All references supporting the assessment report should be attached as a separate document (using appropriate template) and, if applicable, including in a separate section the references which were read but do not support the assessment report.