EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Matricaria recutita* L., flos and *Matricaria recutita* L., aetheroleum

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Matricaria recutita*, flos *Matricaria recutita*, aetheroleum
Herbal preparation(s)	a) Comminuted herbal substance a1) Essential oil b) Liquid extract (1:1), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5)[1] c) Liquid Extract (1:4.3-5.7), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5) d) Liquid extract (1:1), extraction solvent: ethanol 48% V/V : ammonia solution 10% m/m (39:1) e) Liquid extract (1:1), extraction solvent: ethanol 45% V/V : ammonia solution 10% (14.7:1) f) Dry extract (4-7:1), extraction solvent: ethanol 50% m/m g) Liquid Extract (1:1.7-2.6), extraction solvent: ethanol 48% V/V h) Liquid extract (1:1), extraction solvent: ethanol 55% V/V i) Liquid extract (0.5:1), extraction solvent: ethanol 96% V/V

3 The material complies with the Ph. Eur. monograph (ref. 01/2008:1544).

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	j) Liquid extract (2:1), extraction solvent: ethanol 70% V/V k) Liquid extract (1:4.1-4.6) , extraction solvent: ethanol 55% V/V : Poloxamer 188 (993:3) l) Liquid Extract (1:1.8-2.1), extraction solvent: ethanol 52% V/V : macrogol hydroxystearate (99.5:0.5) m) Liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) n) Liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide). o) Dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) p) Liquid extract (1:2.0-2.8), extraction solvent: propan-2-ol 48% V/V
Pharmaceutical forms	Herbal substance or comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage forms for oral use. Herbal substance or comminuted herbal substance for decoction preparation for oromucosal use or cutaneous use. Herbal preparations in liquid dosage forms for preparation of dilutions for steam inhalation. Herbal preparations in semi-solid dosage forms for cutaneous use. Herbal preparations in liquid dosage forms for use as bath additives. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.
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Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Matricaria recutita* L., flos and *Matricaria recutita* L., aetheroleum. It should be noted that this document is a working document, not yet edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the 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.

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1. Introduction

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

- Herbal substance(s)

Matricaria flowers do not only have a long tradition in Europe. Herbal preparations are used worldwide and it is belonging to the most popular medicinal plants of the world. Accordingly, matricaria flowers have been included into collections of monographs. The most important amongst them are:

- European Pharmacopeia
- German Commission E monographs
- British Pharmacopeia
- British Herbal Pharmacopeia
- ESCOP Monographs
- WHO volume 1
- United States Pharmacopeia 29 / NF24

The botany of matricaria and the phytochemical characterisation of the essential oil was reviewed (Carle and Gomaa 1992a; Carle in HagerRom 2011). The herbal substance constists of the dried capitula with yellow tubular florets, surrounded by a ring of white ligulate florets, which are often found on their own. The sharply conical receptacle of the inflorescence is hollow and has no paleaceous scales.

Definitions in the European Pharmacopoeia:

Matricaria flower, Matricariae flos, monograph 01/2008:0404:

> Dried capitula of *Matricaria recutita* L. (syn. *Chamomilla recutita* (L.) Rauschert).
> Content:
> - blue essential oil: minimum 4 ml/kg (dried drug)
> - total apigenin-7-glucoside: minimum 0.25% (dried drug)
>
> Other names: English: German Chamomile, French: Chamomille allemande, Fleur de chamomile, German: Kamillenblüten
> Synonym: Chamomillae anthodium

Matricaria oil, Matricariae aetheoleum, monograph 01/2008: 1836

> Blue essential oil obtained by steam distillation from the fresh or dried flower-heads or flowering tops of *Matricaria recutita* L. (*Chamomilla recutita* L. Rauschert). There are 2 types of matricaria oil which are characterised as rich in bisabolol oxides, or rich in (−)-α-bisabolol.

Matricaria liquid extract, Matricariae extractum fluidum, monograph 01/2008:1544

> Liquid extract produced from Matricaria flower (Ph. Eur. 01/2008: 0404)
> Content: minimum 0.30% of blue residual oil
>
> The extract is produced using a mixture of 2.5 volumes of a 10% (m/m) solution of ammonia (NH_3), 47.5 volumes of water and 50 volumes of ethanol (96%(V/V)).

Main characteristic constituents of matricaria flowers:

essential oil (0.3 – 1.9%): proazulenes like matricin and matricarin, which are at least partially converted during steam distillation into azulenes like chamazulene (further details see below)
flavonoids (up to 6%) such as apiginin-7-glucoside (0.5%) , apigenin and luteolin
sesquiterpene lactones such as matricin (0.03 - 0.2%)
coumarins (0.01% - 0.08%) such as herniarin and umbelliferone
en-in-dicycloethers
phenolic acid and
polysaccharides

Major constituents of the essential oil:

sesquiterpenes: azulenes (2-18%), especially chamazulene
(-)-alpha-bisabolol (up to 50%)
bisabolol oxides A and B
trans-β-farnesene (up to 45%)
spiroethers (20-30%) (cis- and trans-en-yn-dicycloethers

[Carle in HagerROM2011; Wichtl 2002; Barnes *et al*. 2007; ESCOP 2003; Hänsel and Sticher 2007]

Cultivars and different proveniences of matricaria flowers vary substantially with respect to the composition of constitutents. The monograph on matricaria oil (Ph. Eur. 1836) differentiates between matricaria oils rich in bisabololoxides and those rich in (-)-alpha-bisabolol.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

There are two groups of combination products on the European Market. The first one are combination products containing different parts of *Matricaria recutita* L. adding information to the traditional use of *Matricaria recutita* L. in special pharmaceutical forms and to the safety of these products. Secondarily there are lots of combinations on the European Market, which are combining different plants, adding additional information for the safety of the traditional use of Matricariae flos, essential oils and fluid extracts especially in children. Data concerning the efficacy of these products are excluded here, but those supporting the safety of use are integrated into the assessment but they are specified separately.

1.2. Information about products on the market in the Member States

The regulatory status reflects the situation on the European Market according to a request from 2011.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	seven products and many combinations also as MA
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	two products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response

Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	four products
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one combination
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	two combinations
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	twelve products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one product
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	fifteen products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no response
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	four products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	none
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	one combination

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Sources for this assessment report include DIMDI (Deutsches Institut für Medizinische Dokumentation und Information)-database (including MEDLINE), PubMed, Scifinder, the database of the division for Complementary and Alternative Medicines of the Federal Institute for Drugs and Medical Devices (BfArM) and information received from other member states or submitted as response to the call for scientific data by EMA. The search terms of the herbal substance within the databases were Matricaria, matricaria, German chamomile, Kamille and Kamillenblüten. Chamomille allemande, Fleur de Camomille, Camomilla commune, Manzanilla común, Manzanilla de Aragón, Manzanilla ordinaria. Terms for the constituents of assumed therapeutic activity and the specific diseases or conditions

derived from its traditional use and current indications, supplemented with those expected from non-clinical studies with Matricariae flos, were searched. The languages were restricted to German, English, French, Italian and Spanish.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Matricaria is one of the most popular medicinal plants in Europe. Since ancient times traditional use of herbal preparations from matricaria have been reported. Benedum (2006) summarised historical references including Hieronymus Bock (Kreutterbuch 1539), Leonhard Fuchs (New Kreüterbuch 1543) Pietro Andrea Matthiolus (Compendium de plantis omnibus de quibus scripsit suis in commentariis in Dioscoridem editis1571)., A. Lonicerus (Vollständiges Kräuterbuch 1737), Tabernaemontanus (New Kreüterbuch 1613) Dioscurides mentioned the medical use as well. In conclusion there is a consistency in literature for cutaneous use for wound healing, oral treatment of aphthae and internal use for gastrointestinal complaints and spasmolytic activity.

Consequently matricaria was often subject of scientific research and the results of this research were reviewed (Carle 1987; Carle and Gomaa 1992 b) and led to the development of different monographs.

Quality related monographs in the European Pharmacopoeia:

Matricaria Flower Ph. Eur monograph 01/2008 0404

Matricaria Liquid Extract Ph. Eur monograph 01/2008 1544

Matricaria oil Ph. Eur monograph 01/2008 1836

Monographs related to efficacy and safety:

The Commission E Monograph Matricariae flos BAnz Nr.: 228 from 05.12.1984

The WHO monograph Flos chamomillae published in WHO Monographs on Selected Medicinal Plants - Volume 1 1999

The ESCOP monograph Matricariae flos published in ESCOP Monographs second edition Thieme Verlag Stuttgart 1997

2.2. Information on traditional/current indications and specified substances/preparations in European countries

There are manufacturing procedures, which lead to the evaporation of the essential oil. The amount can be added afterwards even with a stability overage, which has to be assessed during registration procedures.

Austria:

Traditional Use

1) Matricariae flos (tea bags containing 1.0 g or 1.5g) for the preparation of a herbal tea
   Mild gastrointestinal disorders, irritation of the oropharyngeal mucosa and of the upper respiratory tract.

Well-established Use

2) Liquid extract (DER 1:4.0 – 4.5), extraction solvent ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (corresponds

to liquid extract m) (since 2002), as oral liquid and semi-solid dosage form in a strength of about 14.88% in base.

Assessors comment:

The herbal substance and the comminuted herbal preparation used in Europe since centuries are accepted for the traditional use part of the monograph. The extract 2) corresponds to liquid extract m) of the monograph, but 30 years of tradition are not fulfilled in Austria. It corresponds to the German specifications, where a tradition of 30 years is fulfilled.

Belgium:

1) Extract EtOH 38.5% (m/m) 1:4.0-4.5, containing 50 mg bisabolol and more than 150 mg apigenine-7-glucoside (since 1995)

   -topical use as emollient and/or antiseptic
   -topical use as complementary anti-pruritic treatment of dermatologic conditions.
   -oral use in symptomatic treatment of GI disturbances after exclusion of all serious pathologies

2) Extract EtOH 95.4% (v/v) (2.75:1) containing min 20 mg essential oil, min 7 mg levomenol (since 2005)

   For topical use in dermatological conditions after exclusion of all serious pathologies. The product has emollient, anti-pruritic, wound-healing and anti-inflammatory properties and is also used in case of frail capillaries

Assessors comment:

The Belgian extract 1) corresponds to liquid extract m), the extract 2) to the liquid extract n) of the monograph, but for both extracts 30 years of tradition are not fulfilled in Belgium. They correspond to the German specifications, where a tradition of 30 years is fulfilled.

Czech Republic:

1) Matricariae flos
   Oral use: for treatment of mild gastrointestinal complaints associated with minor spasms, bloating and flatulence; inflammatory disorders of gastrointestinal tract
   Oromucosal and cutaneous use: for treatment of minor inflammations of skin or mucosa including bacterial infections in oral cavity and in gingivitis, inflammations in anal or genital area; poor healing and infected wounds; furuncles
2) Matricariae extractum corresponding to Ph. Eur.; 33 g/100 g of the solution (since 1969)
   Oromucosal use: for treatment of inflammations in oral cavity or pharynx
   Oral use: for treatment of mild gastrointestinal complaints
   Cutaneous use: for treatment of weeping or pruritic eczema, to support wounds healing, eczema in anal area
3) Matricariae extractum fluidum 1:4-4.5, extracted with the mixture of 40.08% ethanol (96% (V/V)), 57.69% purified water, 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide (concentration of the individual components of the extraction solvent should differ in case that the extract is prepared from fresh flowers (since 1999)
   Inflammations in the oral cavity and pharynx, paradentosis, acute gingivitis, after tooth extraction and during teething, gums irritation caused by denture; catarrh of larynx, inflammation of vocal cords, sore throat.
4) Matricariae extractum siccum 4.8-6.3:1, ethanol 95.4 % (V/V); (not included as originating from 1999; there is no tradition of medical use for 30 years) 10 mg/1 g of the ointment

For adjuvant treatment of minor wounds, skin inflammations, sunburns and burns after UV or RTG irradiation, for adjuvant therapy of venous ulceration and decubits, for treatment of inflammations in anal or genital area, lips inflammations and inflammations of nipples during breastfeeding; for treatment of dry eczema.

Assessors comment:

The herbal substance used in Europe since centuries is accepted for the traditional monograph.
The time frame is not fulfilled for the herbal preparations 2 (corresponds to liquid extract b)) and 3 (corresponds to liquid extract m)), but they correspond to German extracts having a tradition of 30 years and are therefore uptaken. Herbal preparation 4 does not fulfil the criteria of tradition.

Germany: (for date of licensing see table below)

1) Liquid extract (1:1), extraction solvent: ethanol 48% V/V : ammonia solution 10% m/m (39:1) (corresponds to liquid extract d))

   As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival.
   As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.
   For inhalation for a supportive therapy of inflammations and irritations of the respiratory tract.
   For internal use for a supportive therapy of griping pains and inflammations in the gastro-intestinal tract.

2) Dry extract (4-7:1), extraction solvent: ethanol 50% m/m (corresponds to dry extract f))
   Skin inflammations after ultraviolet irradiation (sun burn)

3) Liquid extract (1:4.0-4.5), extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (corresponds to liquid extract m))

   For compresses, irrigation or bathes of inflammations of the skin or mucosa
   As a hip bath
   - in inflammations in the anal area and in the area of the genital organs,
   - in anal pruritus,
   - for relief of complaints in haemorrhoids, anal fissures, anal and perianal eczema,
   - after anogenital surgery,
   - for postoperative therapy of vaginal wounds and episiotomy.

4) Dry extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (corresponds to liquid extract n))
   For after-care following a local corticosteroid therapy of skin inflammations like divers eczema for example
   - contact eczema,
   - occupational eczema,
   - eczema in children,
   - atopic eczema.

5) Liquid extract (1:1.7-2.6), extraction solvent: ethanol 48% V/V (corresponds to liquid extract g))
   For internal use for griping pains and inflammations in the gastro-intestinal tract.
   For inhalation in inflammations and irritations of the upper respiratory tract.

As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival.
As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.

6) Liquid extract (1:1), extraction solvent: ethanol 45% V/V : ammonia solution 10% (14.7:1) (corresponds to liquid extract e))
For internal use for griping pains and inflammations in the gastro-intestinal tract.
For inhalation in inflammations and irritations of the respiratory tract.
As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival.
As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.

7) Liquid extract (1:1), extraction solvent: ethanol 55% V/V (corresponds to liquid extract h))
For cutaneous use as an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.
For inhalation in inflammations and irritations of the respiratory tract.

8) Liquid extract (1:4.1-4.6), extraction solvent: ethanol 55% V/V : Poloxamer 188 (993:3) (corresponds to liquid extract k))
For internal use in griping pains and inflammations in the gastro-intestinal tract.
For cutaneous use for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.
For inhalation in inflammations and irritations of the respiratory tract.

9) Liquid extract (1:4.3-5.7), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5) (corresponds to liquid extract c))
Inflammations of the skin and of the oropharyngeal mucosa.

10) Liquid extract (1:1.8-2.1), extraction solvent: ethanol 52% V/V : macrogol hydroxystearate (99.5:0.5) (corresponds to liquid extract l))
As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival.
As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.
For inhalation for a supportive therapy of inflammations and irritations of the respiratory tract.
For internal use for griping pains and inflammations in the gastro-intestinal tract.

11) Liquid extract (1:2.0-2.8), extraction solvent: propan-2-ol 48% V/V
(corresponds to liquid extract p)
As a full or partial bath, an irrigation, rinsing or compress for
- inflammations of the skin or mucosa,
- bacterial skin diseases like infeted wounds and
-post-treatment of opened abscessus and furuncles.
As a hip bath for
- inflammations in the anal area,
- anal pruritus,
- after surgery,

- for inflammations in the area of the external genital organs,
- for postoperative therapy of vaginal wounds and episiotomy,
- for relief of complaints in haemorrhoids,
- for anal fissures, anal and perianal eczema.

12) Liquid extract (1:1), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5) (corresponds to liquid extract b))
For internal use for griping pains and inflammations in the gastro-intestinal tract.

13) Dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (corresponds to dry extract o))
Inflammations of the skin or mucosa, inflammations in the anal area and in the area of the genital organs.

14) Matricaria flos infusion: (corresponds to comminuted herbal substance a)
For internal use for cramps and inflammations in the gastro-intestinal tract
For cutaneous and oromucosal use in inflammations of the skin or mucosa, including mouth and teeth
For inhalation in inflammations and irritations of the respiratory tract
For cutaneous use in inflammations in the anal area and in the area of the genital organs as bathes and irrigations

15) Liquid extract (1:4.0-4.5), extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide), 98.91 g in 100 g
For internal use for griping pains and inflammations in the gastro-intestinal tract.
For inhalation in inflammations and irritations of the upper respiratory tract.
As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival.
As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.

16) Matricariae aetheroleum: Since 1976 there are different bath additives containing Matricariae aetheroleum in a strength of 125-500 mg/100 g bath additive in medicinal use.
For bathes and irrigation of irritations of skin and mucosae in the anal and genital region

Assessors comment:

The following extracts are accepted for traditional use:

Number of extract	**MA since**	**monograph**
1)	1976	Liquid extract d)
2)	1976	Dry extract f)
3)	1976	Liquid extract m)
4)	1983	Liquid extract n)
5)	1976	Liquid extract g)
6)	1976	Liquid extract e)
7)	1976	Liquid extract h)
8)	1976	Liquid extract k)
9)	1976	Liquid extract c)
10)	1990, GDR product 1983	Liquid extract l)
11)	1976	Liquid extract p)

12)	1976	Liquid extract b)
13)	1976	Dry extract o)
14	1982	Comminuted herbal substance a)
15)	1978	Liquid extract m)
16)	1976	Matricaria aetheroleum

Former GDR (German Democratic Republic) products have been a long time on the GDR Market, but where listed only after the German reunification. In a list from 1983 the ointment is already listed and can therefore be accepted traditionally for the monograph (Arzneimittelverzeichnis der DDR 1983 – List of medicinal products of the German Democratic Republic).

Latvia:

Dry chamomillae flower extract, (15-25:1), extraction solvent: ethanol 95.4% V/V
(authorised in 2004)

Adjuvant treatment of small inflamed wounds:
- inflammation of the skin, e.g., mild sunburn, or following X-ray or UV irradiation;
- leg ulcers or decubitus ulcers – as supportive therapy;
- inflammation in the area of the lips and oral mucosa;
- inflammation around the nipples in breast feeding woman;
-soreness and diaper dermatitis in infants and small children;
- skin and mucosal inflammation in the anal and genital region, e.g., anal fissures or perianal abscesses;
- inflammatory and bacterial skin diseases;
- follow up treatment of eczema (e.g., atopic eczema), particularly where skin is dry

Assessors comment:

This Latvian extract is not introduced into the monograph due to a lacking tradition of 30 years.

Poland:

1 – 10) Chamomillae anthodium (before 1980)

Orally in spastic conditions and mild inflammatory conditions of the intestine. Orally as antispasmodic and mild anti-inflammatory in intestinal complaints. Orally in spastic complaints and mild intestine inflammatory conditions. Orally in abdominal cramps and inflammations of intestine.

In mild spastic complaints of intestine, in bloating, as antispasmodic and anti-inflammatory. Traditionally in spastic complaints and mild intestine inflammatory conditions. Traditionally in intestinal complaints like: mild spastic conditions, bloats, belching. Traditionally in gastrointestinal complaints, light abdominal cramps, filling of fullness, bloating.

Cutaneously in inflammations of skin and mucosa (oral cavity and gingiva). Cutaneously in light inflammatory conditions, skin and mucosa irritations (oral cavity and gingival), anal and genital area.

Cutaneously in mild inflammatory conditions of skin and mucosa, oral cavity and throat, for compresses on skin and for washings (also of anal area). Cutaneously for washings in mild inflammatory conditions of skin and mucosa.

Cutaneously in skin and oral mucosa (oral cavity and gingival) inflammations.

11) Chamomillae anthodii extractum (1:5, ethanol) (not included into the monograph, period of tradition is > 15 years, but shorter than 30 years, exact solvent concentration is missing)

Traditionally orally in mild intestinal complaints, spastic states and bloats. Topically in cutaneous, mucosal inflammations, oromucosal, throat and gingival inflammations.

12) Chamomillae anthodii extractum (1:1; ethanol-water) (not included into the monograph, period of tradition is > 15 years, but shorter than 30 years, exact solvent concentration is missing)
First degree burns (also solar), bedsores, minor abrasions.

13) Chamomillae anthodii extractum fluidum (0.5:1, 96% V/V) ethanol) (corresponds probably to liquid extract i), exact solvent 96% V/V) (before 1980)
Orally as mild spasmolytic and carminative and auxiliary anti-inflammatory in mild inflammatory conditions. Topically in skin inflammatory conditions, in oral cave in oral and gingival inflammatory conditions.

14) Chamomillae anthodii extractum fluidum (2:1, ethanol 70% V/V) (corresponds to liquid extract j)) (before 1980)
Traditionally cutaneously in skin and oral cavity (oromucosal, throat, gingival) inflammations. Orally as auxillary spasmolytic, carminative and anti-inflammatory in gastrointestinal inflammations.

15) Chamomillae unguentum) (not included into the monograph, period of tradition is > 15 years, but shorter than 30 years, details are not available)
Traditionally in skin inflammations.

Assessors comment:

The herbal substance is uptaken, the extracts 13 (corresponds to liquid extract i)) and 14 (corresponds to liquid extract j) fulfil the tradition of over 30 years, the extracts 11 and 15 do not fulfil the tradition and specifications are lacking.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Information on medicinal products

Herbal preparation	Indication	Strength Posology Duration of use
Liquid extract EtOH 38.5% m/m (1:4.0-4.5), containing 50 mg bisabolol and apigenine-7-glucoside min 150 mg liquid extract m) Belgium 1)	-topical use as emollient and/or antiseptic -topical use as complementary anti-pruritic treatment of dermatologic conditions -oral use in symptomatic treatment of GI disturbances after exclusion of all serious pathologies	after dilution: oral use: 2 to 3 ml in cup of lukewarm water, 3-4 times/d; no administration to children <12 y cutaneous use / bath additive: irrigation, wound dressings and partial baths: 15 ml/l; full bath: 2 x 15 ml (or more, depending on need) duration of use: 10 min use as mouthwash: 2-3 ml to max 5 ml in half a cup of lukewarm water; gargle for 1-2 min pure (no dilution): oromucosal use: dab acute infections in mouth
Extract EtOH 95.4% V/V (2.75:1) containing min 20 mg essential oil, min 7 mg levomenol liquid extract n) Belgium 2)	for topical use in dermatological conditions after exclusion of all serious pathologies. The product has emollient, anti-pruritic, wound-healing and anti-inflammatory properties and is also used in case of frail capillaries.	apply a thin layer 2 to 3 times per day or following the advice of the medical doctor. Information on the strength of the herbal preparation in the finished product
Dry chamomillae flower extract, (15-25:1), extraction solvent: ethanol 95.4% V/V Not accepted; <30ys. Latvia	- Adjuvant treatment of small inflamed wounds: - inflammation of the skin, e.g., mild sunburn, or following X-ray or UV irradiation; - leg ulcers or decubitus ulcers – as supportive therapy; - inflammation in the area of the lips and oral mucosa; - inflammation around the nipples in breast feeding	Ointment 4.3 mg/g Cutaneous use Apply several times per day

	woman; - -soreness and diaper dermatitis in infants and small children; - skin and mucosal inflammation in the anal and genital region, e.g., anal fissures or perianal abscesses; - inflammatory and bacterial skin diseases; - follow up treatment of eczema (e.g., atopic eczema), particularly where skin is dry	
Liquid extract (1:1), extraction solvent: ethanol 48% V/V : ammonia solution 10% m/m (39:1) liquid extract d) Germany 1)	As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and sitz bath or irrigation of inflammations in the anal area and in the area of the genital organs. For inhalation for a supportive therapy of inflammations and irritations of the respiratory tract. For internal use for a supportive therapy of griping pains and inflammations in the gastro-intestinal tract.	1 ml (= 20 drops) contains 1 ml liquid extract cutaneous use in adults, adolescents and children from six years of age: skin inflammations: several times daily compresses and irrigations 1 ml /100 ml water or several times daily partial bathes 5 ml /100 ml inflammations of the mucosa, the oral cavity and the gingival: several times daily irrigate or gargle with a solution of 1 ml in 100 ml water inflammations in the anal area and in the area of the genital organs: several times daily irrigations with a solution of 1 ml in 100 ml water or several times daily sit bath with 5 ml per 1 l water Inhalation in adults, adolescents and children from six years of age: Put several times daily 1 ml per 100 ml water in a bowl with hot water and inhale vapour under a towel. Internal use in adults, adolescents and children from 12 years of age: 3 to 4 times daily 60 drops (3 ml)/150 ml water

Dry extract (4-7:1), extraction solvent: ethanol 50% m/m dry extract f) Germany 2)	Skin inflammations after ultraviolet irradiation (sun burn).	100 g (= corresponding to 98.1 ml) liquid contain 0.4668 g dry extract children from six years of age, adolescents and adults: Put 2 to 3 times daily drop by drop on the skin thinly and work it in lightly. Only dab it on strongly sensitive skin.
Liquid extract (1:4.0-4.5), extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide), 98.91 g in 100 g liquid extract m) Germany 3)	For impregnated dressings, irrigation or bathes of inflammations of the skin or mucosa. As a hip bath - in inflammations in the anal area and in the area of the genital organs, - in anal pruritus, - for relief of complaints in haemorrhoids, anal fissures, anal and perianal eczema, - after anogenital surgery, - for postoperative therapy of vaginal wounds and episiotomy.	100 ml (= 97 g) bath additive contains 97 g extract Cutaneous use in adults, adolescents and children from six years of age: For impregnated dressings and irrigations: 45 ml per 1 l water, 1 to 2 times daily. For partial and hip bathes: 30 ml per 1 l water, 1 to 2 times daily
Specification as liquid extract m) Germany 15)	For internal use for griping pains and inflammations in the gastro-intestinal tract. For inhalation in inflammations and irritations of the upper respiratory tract. As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.	Oral Use: Adolescents, adults, elderly Single dose: 5 ml in 100 ml water Daily dose: up to 4 times daily Children from 6-12 years of age Single dose: 2-3 ml in 100 ml water Daily dose: up to 4 times daily For inhalation Adolescents, adults, elderly Single dose: 20 ml per 1 l hot water Daily dose: 1-2 times daily Gargling rinsing mouth and throat

		Adolescents, adults, elderly Single dose: 5 ml per 100 ml warm water Daily dose: 3 to several times Adolescents, adults, elderly For washings, impregnated dressings and irrigations: Single dose: 45 ml per 1 l water Daily dose: 1-2 times daily For partial bath or hip bath: Single dose: 30 ml per 1 l water Daily dose: 1-2 times daily
Liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) Liquid extract n) Germany 4)	- For after-care following a local corticosteroid therapy of skin inflammations like divers eczema for example - contact eczema - occupational eczema - eczema in children - atopic eczema	1 g cream contains 20 mg extract also for use in infants and toddlers Put it on the skin thinly 3 times daily, if symptoms improve. Use of 2 times daily is sufficient.
liquid extract (1:1.7-2.6), extraction solvent: ethanol 48% V/V liquid extract g) Germany 5)	For internal use for griping pains and inflammations in the gastro-intestinal tract. For inhalation in inflammations and irritations of the upper respiratory tract. As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.	100 ml solution contain 95.8 g extract 1 ml corresponds to 20 drops children from six years of age, adolescents and adults For internal use: children between 6 and 12 years of age: 3 to 4 times daily 13-20 drops/150 ml adults and adolescents: 3 to 4 times daily 30 drops/150 ml) For inhalation: 15 ml/1 l hot water 1 to 2 times daily For cutaneous use and for a bath: For impregnated dressings and irrigation and for partial or hip bathes 15 ml per 1 l hot water several times daily

liquid extract (1:1), extraction solvent: ethanol 45% V/V : ammonia solution 10% (14.7:1) liquid extract e) Germany 6)	For internal use for griping pains and inflammations in the gastro-intestinal tract. For inhalation in inflammations and irritations of the respiratory tract. As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs.	100 g solution contain 50.075 g liquid extract For internal use: children between 6 and 12 years of age: up to 4 times daily 2.5 ml/150 ml water Adults and adolescents: up to 4 times daily 5 ml/150 ml For impregnated dressings and irrigation: 20 ml per 1 l water several times daily For partial and hip bathes: 10 ml per 1 l water several times daily For mouth rinsing or gargling: 2.5 ml in 125ml water 3 to 4 times daily For inhalation: 5 ml/150 ml water
Liquid extract (1:1), extraction solvent: ethanol 55% V/V Liquid extract h) Germany 7)	For cutaneous use as an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs. For inhalation in inflammations and irritations of the respiratory tract.	100 ml liquid contain 100 ml liquid extract 1 ml corresponds to 30 drops Oral use (also for mouth rinsing or gargling): Up to 4 times daily/150 ml warm water Children between 6 and 12 years of age: 15-30 drops Adolescents and adults: 30-60 drops Inhalation and vapour bath of the face: 15 ml per 1 l hot water 1 to 3 times daily Impregnated dressings and irrigation in the anal and genital area: 15 ml per 1 l water, one to several times daily partial and hip bathes:15-30 ml in 5 l warm water, one to several times daily
Liquid extract (1:4.1-4.6) , extraction solvent: ethanol 55% V/V : Poloxamer 188 (993:3)	For internal use in griping pains and inflammations in the gastro-intestinal tract. For cutaneous use for impregnated dressings, to	100 ml liquid (= 93.45 g) contain: 93.45 g extract For impregnated dressings and irrigations: 40 ml per 1 l water, one to several times daily

Liquid extract k) Germany 8)	irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs. For inhalation in inflammations and irritations of the respiratory tract.	For partial and hip bathes: 20 ml per 1 l water, one to several times daily For mouth rinsing or gargling: 5 ml in 100 ml water 3 times daily For oral use: 5 ml/150 ml warm water up to 3 to 4 times daily For inhalation: 40 ml per 1 l hot water 1 to 2 times daily
liquid extract (1:4.3-5.7), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5) Liquid extract c) Germany 9)	inflammations of the skin and of the oropharyngeal mucosa	100 ml liquid contain 100 ml extract For oropharyngeal inflammations gargle or rinse with the fresh infusion 3 to 4 times daily. For inflammation of the skin wash or irrigate or put a impregnated dressing with the infusion. 10 ml with 150 ml hot water
liquid extract (1:1.8-2.1), extraction solvent: ethanol 52% V/V : macrogol hydroxystearate (99.5:0.5) Liquid extract l) Germany 10)	As an additive for impregnated dressings, to irrigation or rinsing of inflammations of the skin or mucosa including the oral cavity and the gingival. As an additive to partial bath and hip bath or irrigation of inflammations in the anal area and in the area of the genital organs. For inhalation for a supportive therapy of inflammations and irritations of the respiratory tract. For internal use for griping pains and inflammations in the gastro-intestinal tract	100 g liquid contain 100 g extract. 1 g = ca. 30 drops Inhalation: In inflammations and irritations of the respiratory tract inhale with 10-20 ml/1 l; 1 to 3 times daily for ca. 5 min For mouth rinsing or gargling: In inflammations of the oral mucosa and the gingiva 20-30 drops/75 ml several times daily hip bathes and irrigations: In inflammations in the anal and genital area 7.5-15 ml per 1 l water one to several times daily Impregnated dressings, irrigations and partial bathes: In skin inflammations 10-20 ml per 1 l water if necessary one to several times daily For internal use

		In cramps and inflammations of the gastro-intestinal tract up to 4 times daily on a glass water (150 ml): children between 6 and 12 years of age 20 drops, adolescents and adults 30 drops
liquid extract (1:2.0-2.8), extraction solvent: propan-2-ol 48% V/V Liquid extract p) Germany 11)	As a full or partial bath, an irrigation, rinsing or compress for - inflammations of the skin or mucosa - bacterial skin diseases like infected wounds - post-treatment of opened abscesses and furuncles As a hip bath for - inflammations in the anal area - anal pruritus - after surgery - inflammations in the area of the external genital organs, - postoperative therapy of vaginal wounds and episiotomy - relief of complaints in haemorrhoids, - for anal fissures, anal and perianal eczema	100 ml solution contains 94.2 g extract For infants, children, adolescents and adults Impregnated dressings and irrigation 20 ml per 1 l water 1 to several times daily. Partial and sit bath 20 – 40 ml in 20-40 l water, once daily Bath for infant and children 10 – 20 ml in 10-20 l water, once daily. Full bath 30 ml in 150 l water, once daily
liquid extract (1:1), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5) Liquid extract b) Germany 12)	For internal use for griping pains and inflammations in the gastro-intestinal tract.	100 g liquid (= 101 ml) contain 20 g liquid extract Adolescents and adults: 10 ml in one glass of warm water (ca. 150 ml), 3 to 4 times daily
dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) Dry extract o) Germany 13)	inflammations of the skin or mucosa, inflammations in the anal area and in the area of the genital organs	1 g cream contains 3.94 mg dry extract. Apply a thin layer several times daily.

Matricariae aetheroleum Germany 15)	As a full or partial bath, an irrigation, rinsing or impregnated dressing for: - inflammations of the skin or mucosa - bacterial skin diseases like infected wounds - post-treatment of opened abscesses and furuncles. As a hip bath for: - inflammations in the anal area - anal pruritus - after surgery - for inflammations in the area of the external genital organs - postoperative therapy of vaginal wounds and episiotomy - relief of complaints in haemorrhoids, - anal fissures, anal and perianal eczema	several times daily on the relevant parts 0.12-0.5 g essential oil/100 g bath additive: full bath 10-20 ml/80 l hip bath 2-3 ml/10 l
Flos Matricariae Herbal substance a) Austria 1)	mild gastrointestinal disorders, irritation of the oropharyngeal mucosa and of the upper respiratory tract	Herbal tea: 1.5 g 3-4 x daily
Flos Matricariae Herbal substance a) Austria 2	Irritation of the oropharyngeal mucosa and of the upper respiratory tract.	Herbal tea:1.0 g several times daily; throat washing 3 min; inhalation 5-10 min
Matricariae flos Herbal substance a) Czech Republic 1)	Oral use: for treatment of mild gastrointestinal complaints associated with minor spasms, bloating and flatulence; inflammatory disorders of gastrointestinal tract Oromucosal and cutaneous use: for treatment of minor inflammations of skin or mucosa including bacterial infections in oral cavity and in gingivitis, inflammations in anal or genital area; poor healing and infected wounds; furuncles	Herbal tea: -oral use: 1.5 g/250 ml; 3 x daily -oromucosal or cutaneous use, inhalations: 3-4.5 g/250 ml; use several time daily -as a gargle, irrigation or impregnated dressings or for lavation or as a bath

Matricariae flos Comminuted herbal substance a) Germany 14)	For internal use for cramps and inflammations in the gastro-intestinal tract For cutaneous and oromucosal use in inflammations of the skin or mucosa, including mouth and teeth For inhalation in inflammations and irritations of the respiratory tract For cutaneous use in inflammations in the anal area and in the area of the genital organs as bathes and irrigations	Oral use: 3 g/150 ml water; 3-4 x daily Gargling, rinsing inhaling, impregnated dressings: 3-10 g Matricariae flos/100 ml water Baths:50 g Matricariae flos/10 l water Children from 6 months to 2 years: Single dose: 0.5-1.0 g Daily dose: 2-4 times Children 2-6 years: Single dose:1.0-2.0 g Daily dose: 2-4 times Children 6-12 years: Single dose: 1.5 - 3.0 g Daily dose: 2-4 times
Matricariae extractum corresponding to Ph.Eur.; 33 g/100 g of the solution Liquid extract b) Czech Republic 2)	Oromucosal use: for treatment of inflammations in oral cavity or pharynx Oral use: for treatment of mild gastrointestinal complaints Cutaneous use: for treatment of weeping or pruritic eczema, to support wounds healing, eczema in anal area	for oral, oromucosal and cutaneous use as a gargle: 1 tea spoon/glass of water, 3-5 x daily for bath or impregnated dressings: 15-30 ml/l of water, compresses every 4-6 hours for 30 min for oral use: ½ - 1 tea spoon/200 ml hot water, 3-4 x daily
Matricariae extractum fluidum (1:4-4.5), extracted with the mixture of 40.08% ethanol (96% (V/V)), 57.69% purified water, 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide Liquid extract m) Czech Republic 3)	inflammations in the oral cavity and pharynx, paradentosis, acute gingivitis, after tooth extraction and during teething, gums irritation caused by denture; catarrh of larynx, inflammation of vocal cords, sore throat	for oromucosal use 3 x daily

Matricariae extractum siccum 4.8-6.3:1, ethanol 95.4% (V/V) Not accepted; <30 ys. Czech Republic 4)	for adjuvant treatment of minor wounds, skin inflammations, sunburns and burns after UV or RTG irradiation, for adjuvant therapy of venous ulceration and decubits, for treatment of inflammations in anal or genital area, lips inflammations and inflammations of nipples during breastfeeding; for treatment of dry eczema	10 mg/1 g of the ointment for cutaneous use several times daily
Chamomillae anthodium Herbal substance Poland 1-10)	Orally in spastic conditions and mild inflammatory conditions of the intestine. Orally in abdominal cramps and inflammations of intestine. Orally as antispasmodic and mild anti-inflammatory in intestinal complaints. In mild spastic complaints of intestine, in bloating, as antispasmodic and anti-inflammatory. Traditionally in intestinal complaints like: mild spastic conditions, bloats, belching. Traditionally in gastrointestinal complaints, light abdominal cramps, filling of fullness, bloating. Traditionally in spastic complaints and mild intestine inflammatory conditions. Cutaneously in inflammatory conditions of skin, mucosa (also oral cavity). Cutaneously in mild inflammatory conditions of oral cavity and throat, for compresses on skin and for washings (also of anal area). Cutaneously for washings in mild inflammatory conditions of skin and mucosa. Cutaneously in light inflammatory conditions, skin and mucosa irritations (oral cavity and gingival), anal and genital area.	Herbal tea 2.4-4 g / 2-4 x daily as tea -For skin and mucosa washings use infusion -washing mucosa of oral cavity or for compresses on skin. - For washing mucosa and cutaneous use infusion prepared (3-10 g) - hip bath (4.5 g/1 l)

	Cutaneously in skin and oral mucosa (oral cavity and gingival) inflammations.	
Chamomillae anthodii extractum (1:5, ethanol) Not accepted <30 ys. Poland 11)	Traditionally orally in mild intestinal complaints, spastic states and bloats. Topically in cutaneous, mucosal inflammations, oromucosal, throat and gingival inflammations.	Orally 2.5-5 ml /50-100 ml 3 x daily Cutaneously for washings and compresses, 5 ml/100 ml (or 10%) mouth washings, infusion 3%
Chamomillae anthodii extractum (1:1; ethanol-water) Not accepted; <30 ys. Poland 12)	First degree burns (also solar), bedsores, minor abrasions.	Ointment: Smear skin 1-3 x daily
Chamomillae anthodii extractum fluidum (0.5:1, ethanol) Liquid extract i) Poland 13)	Orally as mild spasmolytic and carminative and auxiliary anti-inflammatory in mild inflammatory conditions. Topically in skin inflammatory conditions, in oral cave in oral and gingival inflammatory conditions.	Orally 3-4 x daily 5 ml in water. Cutaneously in 10% solution in boiled water.
Chamomillae anthodii extractum fluidum (2:1, ethanol 70% V/V) Liquid extract j) Poland 14)	Traditionally cutaneously in skin and oral cavity (oromucosal, throat, gingival) inflammations. Orally as auxillary spasmolytic, carminative and anti-inflammatory in gastrointestinal inflammations.	Orally 2.5-5 ml /50-100 ml 3 x daily Cutaneously for washings and impregnated dressings, 5ml/100 ml .(or 10%) mouth washings, infusion 3%
Chamomillae unguentum Not accepted <30 ys. Lacking specification Poland 15)	Traditionaly in skin inflammations.	Smear skin 1-3 x daily

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

The herbal preparations uptaken in the monograph reflect the ones reported by MS. For which preparation the tradition is accepted is to be seen in the table 2.2 under “Active substance” as well as in the table at the end of monograph and Assessment Report within the column “Extracts”.

Table 2.3: Overview of evidence on period of medicinal use AR Matricaria in the order of the monograph

Used abbreviations:

Abbreviations: SD: single dose, DD: daily dose, P:partial bath, F: full bath

Herbal preparation **Pharmaceutical form**	**Indication**	**Strength** **Posology**	**Period of medicinal use**
a) Comminuted herbal substance Herbal tea; oral use, oromucosal use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 1.5-4 g DD: 3-4 times Children 6-12 years SD:1.5-3.0 g DD: 2-4 times Children 2-6 years SD:1.0-2.0 g DD: 2-4 times Children 6 months-2 years SD:0.5-1.0 g DD: 2-4 times	PL before 1980 Dorsch 1993
	- relief of symptoms of common cold	Adolescents; Adults, Elderly 3-10 g/100 ml water DD:1-2 times Children 6-12 years SD:2-5 g/100 ml water DD:1-2 times	Standard Marketing authorisation DE 1982
	- minor ulcers and inflammations of the mouth and throat	Gargling/rinsing Adolescents, Adults, Elderly SD: 1 g DD several times	PL before 1980
	- irritations of skin and mucosae in the anal and genital region	Irrigation Adolescents, Adults, Elderly SD: 4.5-5 g/l water DD: several times	Standard Marketing Authorisation DE 1982
	- minor inflammation of the skin		PL before 1980

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	(sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 2.4-4 g/150 ml water DD several times	
b) Liquid extract (1:1), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5)[2] Liquid for oral use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 10 ml /150 ml water DD: 3-4 times	DE 1976
c) Liquid Extract (1:4.3-5.7), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% V/V (50:47.5:2.5)	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 10 ml/150 ml water DD: 3-4 times	DE 1976
Liquid for oromucosal use or cutaneous use.	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 10 ml/150 ml water DD: 3-4 times	DE 1976
d) Liquid extract (1:1), extraction solvent: ethanol 48% V/V : ammonia solution 10% m/m (39:1) Liquid for oral, inhalative, oromucosal, cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 3 ml/150 ml water DD: 3-4 times	DE 1976
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD: 1.5 ml/150 ml water DD: 1-2 times	DE 1976
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 1.5 ml/150 ml water DD: several times	DE 1976
	- irritations of skin and mucosae in the anal and genital region	Adolescents, Adults, Elderly SD: 1.5 ml/150 ml water DD: several times	DE 1976
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 1.5 ml/150 ml water DD: several times	DE 1976

3 The material complies with the Ph. Eur. monograph (ref. 01/2008:1544).

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
e) Liquid extract (1:1), extraction solvent: ethanol 45% V/V : ammonia solution 10% (14.7:1) Liquid for oral, inhalative, oromucosal, cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 5 ml/150 ml water DD: up to 4 times Children 6-12 years SD: 2.5 ml/150 ml water DD: up to 4 times	DE 1976
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD: 5 ml/150 ml water DD: several times	DE 1976
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 2.5 ml/125 ml water DD: 3-4 times	DE 1976
	- irritations of skin and mucosae in the anal and genital region	Adolescents, Adults, Elderly SD: 10 ml/l water DD: several times	DE 1976
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 20 ml/l water DD: several times daily	DE 1976
f) Dry extract (4-7:1), extraction solvent: ethanol 50% m/m Liquid for cutaneous us	- minor inflammation of the skin (sunburn)	Adolescents, Adults, Elderly SD: few drops on affected skin DD: several times	DE 1976
g) Liquid Extract (1:1.7-2.6), extraction solvent: ethanol 48% V/V Liquid for oral, inhalative and cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 1.5 ml/150 ml water DD: 3-4 times Children 6-12 years SD: 0.7-1 ml DD:3-4 times	DE 1976
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD: 15 ml/l water DD: 1-2 times	DE 1976
	- irritations of skin and mucosae in the anal and genital region	Adolescents, Adults, Elderly SD: 15 ml/l water DD: several times	DE 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 15 ml/l water DD: several times	DE 1976
h) Liquid extract (1:1), extraction solvent: ethanol 55% V/V Liquid for oral, inhalative, oromucosal and cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 1-2 ml/150 ml water DD: up to 4 times Children 6-12 years: SD: 0.5-1 ml /150 ml water DD: up to 4 times	DE 1976
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD: 15 ml/l water DD: 1-3 times Children 6-12 years SD: 0.5 – 1 ml DD: up to 4 times	DE 1976
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 1-2 ml DD: up to 4 times Children 6-12 years SD: 0.5-1 ml DD: up to 4 times	DE 1976
	- irritations of skin and mucosae in the anal and genital region	Impregnated dressings and irrigation: Adolescents, Adults, Elderly SD: 15 ml/l water DD: 1-several times Partial bathes: SD: 15-30 ml/5 l water DD: 1-several times	DE 1976
i) Liquid extract (0.5:1), extraction solvent: ethanol 96% V/V Liquid for oral, oromucosal and cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 5 ml/150 ml water DD: 3-4 times	PL before 1980
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 5 ml/150 ml water DD: 3-4 times	PL before 1980

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 10 ml+90 ml hot water DD: several times	PL before 1980
j) Liquid extract (2:1), extraction solvent: ethanol 70% (V/V) Liquid for oral, oromucosal and cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 2.5-5 ml/50-100 ml water DD:3 times	PL before 1980
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 2.5-5 ml/50-100 ml water DD:3 times	PL before 1980
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD: 5-10 ml/100 ml water DD: several times	PL before 1980
k) Liquid extract (1:4.1-4.6) , extraction solvent: ethanol 55% V/V : Poloxamer 188 (993:3) Liquid for oral, inhalative, oromucosal, cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 5 ml/150 ml water DD:3-4 times	DE 1976
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD: 40 ml/l water DD:1-2 times	DE 1976
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 5 ml/100 ml water DD: 3 times	DE 1976
	- irritations of skin and mucosae in the anal and genital region	Washing , dressing Adolescents, Adults, Elderly SD: 40 ml/l water DD: 1-several times Partial bath: SD: 20 ml/l water DD: 1-several times	DE 1976
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents,Adults, Elderly SD: 40 ml/l water DD: 1-several times	DE 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
l) Liquid Extract (1:1.8-2.1), extraction solvent: ethanol 52% V/V : macrogol hydroxystearate (99.5:0.5) Liquid for oral, inhalative, oromucosal, cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 1 g/150 ml water DD: up to 4 times Children 6-12 years SD:0.7 g/150 ml water DD: up to 4 times	DE 1990, GDR 1983
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD:10-20 ml/l water DD: 1-3 times	DE 1990, GDR 1983
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 0.7-1 g/75 ml water DD: several times	DE 1990, GDR 1983
	- irritations of skin and mucosae in the anal and genital region	Washing dressing Adolescents, Adults, Elderly SD:10-20 ml/l water DD: 1-several times hip bathes and irrigations: Adolescents, Adults, Elderly SD:7.5-15 ml/l water DD: 1-several times	DE 1990, GDR 1983
m) Liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) Liquid for cutaneous use	- symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, Adults, Elderly SD: 5 ml/100 ml water DD: up to 4 times Children 6-12 years SD:2-3 ml /100 ml water DD: up to 4 times	DE 1978
	- relief of symptoms of common cold	Adolescents, Adults, Elderly SD:20 ml/l water DD:1-3 times	DE 1978
	- minor ulcers and inflammations of the mouth and throat	Adolescents, Adults, Elderly SD: 5 ml /100 ml water DD: up to 4 times	DE 1978

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	- irritations of skin and mucosae in the anal and genital region	Adolescents, Adults, Elderly SD: 45 ml/l water DD:1-2 times	DE 1976
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly SD:partial bath: 30ml/l water DD:1-2 times	DE 1976
n) Liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) Liquid for cutaneous use	- irritations of skin and mucosae in the anal and genital region - minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	For both indications Adolescents, Adults, Elderly Children 6-12 years Children 2-6 years Children 4 weeks-2 years Children newborn – 4 weeks cream corresponds to 8% herbal substance DD:2-3 times	DE 1983
o) Dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) Semi-solid dosage form for cutaneous use	- irritations of skin and mucosae in the anal and genital region	Adolescents, Adults, Elderly ointment corresponds to 5.5% herbal substance DD: 2-3 times	DE 1976
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Adolescents, Adults, Elderly ointment corresponds to 5.5% herbal substance DD: 2-3 times	DE 1976
p) Liquid extract (1:2.0-2.8), extraction solvent: propan-2-ol 48% V/V Liquid for cutaneous use	- irritations of skin and mucosae in the anal and genital region	Partial bathes: Adolescents, Adults. Elderly SD:partial bath: 20-40 ml/20-40 l water DD: 1 times	DE 1976
		Full bathes: Adolescents, Adults, Elderly SD:full bath: 30 ml/150 l water DD:1 times	DE 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
		Children 2-12 years SD:10-20 ml/10-20 l water DD:1 times	DE 1976
	- minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles)	Irrigations, dressings: Adolescents, Adults, Elderly SD: 20 ml/l water DD: 1-several times	DE 1976

If no amount of water is given, the amount of preparation is calculated /150 ml warm to hot water.
If extracts are signed connected to numbers, the numbers address the different indications.

The numeracy after the brackets in the extract column reflect the number of the relevant indications.

3. Non-Clinical Data

Many pharmacological studies have been published regarding preparations of Matricariae flos, Matricaria oil and their constituents. A systematic review of all these studies will not be attempted here, rather a selection of studies with emphasis on studies with relevance for the plausibility of the traditional use of the different preparations and their different methods of administration.

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

Over 120 constituents have been identified in matricaria flowers (Mann and Staba 1986). Apigenin (16.8%), quercetin (9.9%), patuletin (6.5%), luteolin (1.9%) and their glycosides are the major flavonoids present in the total flower, although their relative concentrations vary within the different flower parts (Mann and Staba 1986; Mulinacci *et al.* 2000; Barene *et al.* 2003). Mulinacci reported the presence of large amounts (39.1%) of ferulic and caffeic acids as well as unidentified phenolic derivatives (25.8% of the total flower). The coumarines herniarin and umbelliferone (in a ratio of 1:5) add up to 0.1% of the constituents.

The yield of essential oil from the flowers is minimum 0.4% (Phr Eur). The main constituents of the essential oil includes the terpenoids α-bisabolol and its oxides (≤78%) and azulenes including chamazulene (1-15%) (Matos *et al.* 1993*;* Mimica-Dukic *et al.* 1993; Stanev *et al. 1996,* Pino *et al.* 2002; Pino *et al.* 2003).
Teas brewed from matricaria flowers contain 10-15% of the essential oil available in the flower. The coumarines herniarin and umbelliferone are soluble in hot water and the amounts obtained from frequent consumption of teas or infusions are not negligible (Mulinacci *et al.* 2000).

3.1.1. Primary Pharmacodynamics

Anti-inflammatory effects

In vitro:

Isolated substances:
The therapeutic potential of apigenin as an anti-inflammatory agent contributing to the clinical anti-inflammatory efficacy of matricaria extracts was demonstrated *in vitro* through its ability to interfere with leukocyte adhesion and adhesion protein upregulation in human endothelial cells (Gerritsen *et al.* 1995). It also inhibited interleukin 1α (IL-1) induced prostaglandin synthesis, tumor necrosis factor α (TNFα), induced IL-6 and IL-8 production and blocked adhesion of leukocytes to cytokine treated endothelial cells. In murine macrophages 3.7 and 37 µM apigenin significantly inhibited LPS-induced IL-6 production in a dose dependent manner, but not TNFα (Smolinski and Pestka 2003). Other studies using apigenin in cell culture models have also shown that this flavonoid has inhibitory effects on prostaglandin E2 (PG-E2), cyclooxygenase 2 (COX-2) and nitric oxide production (Liang *et al.* 1999).

Chamazulene has also been shown to inhibit the inflammatory process in vitro (Safayhi *et al.* 1994). At 15 µM chamazulene inhibited the synthesis of leukotriene B4 in stimulated rat peritoneal neutrophilic granulocytes by 50%. In a cell-free system 2 µM chamazulene blocked the chemical peroxidation of arachidonic acid.

Examining histamine release from rat mast cells en-in-dicycloether partly inhibited a protamine sulphate provoked degranulation at concentrations >100 µM, whereas neither chamazulene nor α-bisabolol had any effect. (Miller *et al.* 1996).

In vivo:

Matricaria extracts:

A freeze dried extract of matricaria (no further information available) given to Wistar rats suppressed both, the inflammatory effect and leucocyte infiltration induced by simultaneously given carrageenan and prostaglandin E1 (Shipochliev *et al.* 1981).

In mice fed a diet containing 1.2% (w/w) of an ethyl acetate extract of dried *M. recutita* flower for 11 days, scratching behaviour induced by the compound 48/80 was suppressed in a dose- dependent manner (Kobayashi *et al.* 2005). The extract was prepared with 350 g dried flowers of *Matricaria recutita* extracted with 7 l ethyl acetate twice under sonication for 3 h at 70°C. The extract was filtered and the filtrate evaporated under reduced pressure and freeze dried. (14.0 g extract). The extract at a dose of 100, 300 and 1000 mg/kg dissolved in a vehicle of 10% ethanol, 10% Tween 80 and 80% physiological saline solution were orally administered. Scratching behaviour induced by compound 48/80 was significantly suppressed by the upper two doses ($p=0.05$) with a non altered spontaneous motor activity.

In Swiss mice the topical application of a hydroalcoholic extract of *Matricaria recutita* (20 g flos to 100 ml ethanol 42%V/V) to the inner surface of the ear reduced edema induced by the application of a 2.5% emulsion of croton oil (Tubaro *et al.* 1984). The extract contained: 0.05 mg/ml of (-)-α-bisabolol, 0.45 mg/ml of bisabolol oxides, 0.4 mg/ml apigenin and its glucosides, 0.8mg/ml en-in-dicycloethers, 0.02 mg/ml azulenes). 1 ml of extract corresponds to 50 mg dry extract. The groups with 40 animals each were treated with 0.08; 0.25; 0.75 mg dry extract. Compared to control animals ($n=104$) mice treated with 0.25 mg of matricaria showed 8.5% reduction in edema and those treated with 0.75 mg had a 23.4% reduction. No significant changes were seen in the group treated with 0.08 mg. The effect in the 0.75 mg group was similar to the positive reference treated with 0.45 mg benzydamine used as a positive control. Neither reached the level of reduction induced by 0.15 mg hydrocortisone (56%).

Della Loggia *et al.* (1990) found that topical treatment with an extract of fresh matricaria containing 51.8 mg/100 g bisabolol, 29.6 mg/100 g matricine, and 5.3 mg/100 g apigenin at a dose equivalent to 750 µg of dry product ($n=25$) was as effective as the reference drug 0.60 mg benzydamine ($n=25$) in preventing inflammatioin in mice subjected to croton oil induced edema. The benzydamine, fresh matricaria extract and dried matricaria extract (54.6 mg/100 g bisabolol, 16.4 mg/100 g matricine, 6.3 mg/100 g apigenin; $n=26$) inhibited the inflammatory response by 31.5%; 31.6% and 23.7% respectively compared to the control group ($n=41$).

The antiulcerogenic properties of *Matricaria chamomilla* hydroalcoholic extract (MCE) on ethanol-induced gastric mucosal injury were investigated by Cemek *et al.* (2010) in rats. Airdried *Matricaria recutita* (plant part and status not specified) was pulverized. 100 g plant material was extracted with 1 l Ethanol 37% in a soxhlet apparatus. The extract was lyophilized. Group 1 (7 rats each) received ethanol, groups 2-6 received 25, 50, 100, 200, 400 mg MCE/kg, group 7 received famotidine + ethanol as positive control. After the induction of gastric mucosal injury, all groups were sacrificed; the gastric ulcer index (total ulcer area/total gastric area) was calculated, and malondialdehyde (MDA) and reduced glutathione (GSH) in whole blood and gastric tissue, and serum ascorbic acid, retinol, and beta-carotene levels were measured in all groups. MCE clearly has a protective effect against ethanol-induced gastric mucosal lesions (Control (ethanol) 20.67±1.6; MCE-25+ethanol 18.79±2.8; MCE-50+ethanol 11.87±1.2; MCE-100+ethanol 15.96±1.7; MCE-200+ethanol 8.61±2.7; MCE-400+ethanol 10.29±2.7), and this effect, at least in part, depends upon the reduction in lipid peroxidation and augmentation in antioxidant activity.

Al Hindawi *et al.* 1989 tested *Matricaria recutita* flowers. Approximately 50 g of dried plant material was extracted with 80% ethanol (3 x 500 ml; no information whether V/V or m/m) by shaking for 3 h at room temperature. The supernatant was evaporated at 40°C. The residue was dissolved and resuspended in distilled water using a minimum amount of Tween 80. Each g of the dried extract was equivalent to 4.05 g of the fresh plant material. 400 mg/kg extract reflecting 1.62 g fresh plant equivalent /kg inhibited rat paw edema at 41.1% of control (P>0.01).

Essential oil:

Kobayashi *et al.* (2005) determined the antipruritic effect of the matricaria essential oil. The essential oil groups (100, 300 and 1000 mg/kg) reduced the scratching behaviour significantly with 300 ($p<0.01$) and 1000 mg/kg ($p<0.001$).

Della Loggia *et al.* (1990) found that topical treatment with the matricaria essential oil containing 55.6 mg bisabolol/100 g , 4.7 mg chamazulene/100 g , but no matricine or apigenin at a dose equivalent to 30 µg essential oil showed no effect in preventing inflammatioin in mice subjected to croton oil induced edema (6.6% inhibition n=25).

Isolated substances:

(-)-α-bisabolol was able to decrease leukocyte migration, protein extravasations and the amount of TNF-α to the peritoneal cavity in response to carrageenan induced rat paw edema. Additionally, (-)-α-bisabolol reduced neutrophil degranulation in response to phorbol-myristate-acetate (Rocha *et al.* 2011).

Proinflammatory cytokine production was inhibited in mice treated with 50 mg apigenin/kg for 1 h then injected with stimulant Lipopolysaccharide (LPS) (Smolinski and Pestka 2003). Apigenin inhibited LPS-induced IL-6 (65% less than control) and/or TNFα production (76% less than control) in serum of the mice. Apigenin showed anti-inflammatory activity in carrageenan induced rat paw edema (Al Hindawi *et al.* 1989; Gerritsen *et al.* 1995).

Panés *et al.* (1996) injected male Sprague-Dawley rats intraperitoneally with rTNF (rat Tumor necrosis factor) and induced a significant increase in ICAM-1 expression (intracellular adhesion molecule 1) in different organs (lung 38%, kidneys 29%, liver 67%, heart 197%, skeletal muscle 257%, mesentery 176%).Treatment with apigenin 100 mg/kg significantly decreased ICAM-1 expression after rTNF administration in all organs. It completely abrogated the rTNF induced upregulation in lung, liver and brain. It significantly attenuated the ICAM-1 responses in heart, pancreas and mesentery and blocked ICAM-1 upregulation in skeletal muscle.

Hempel *et al*. (1998) tested constituents of topical Matricaria preparations in inflammations of the mouse ear induced by arachidonic acid, phorbolmyristate acetate and oxazolone. Bisabololoxide A and B showed an anti-inflammatory effect comparable to bisabolol. Matricin and chamazulen ($1x10^{-6}$ molar each) seemed to be a little less effective, but it has to be considered the slow transformation from matricin to chamazulene at the skin. The En-in ether, predominantly the cis form, showed a good anti-inflammatory effect contrarily to in vitro data. Apigenine was more effective than apigenine-7-glycoside. The constituent with known therapeutic activity is according to the data not a single one but the effectiveness results from the interplay of different constituents as described.

In rats, both apigenin and α-bisabolol inhibited the development of gastric ulcers induced by indomethacin, stress and alcohol (Szelenyi *et al.* 1979). In this study, α-bisabolol was also shown to reduce healing times in ulcers induced by either chemical stress or heat coagulation.

Assessors comment:

In vitro pharmacological data for the constituents of matricaria recutita containing extracts and in vivo data for different extracts as well as constituents thereof show in several experiments a decrease of

the inflammatory reaction documented by controls. These data exist not for all herbal preparations included in the monograph. Furthermore the concentrations/dosages used are relatively high.

Wound healing

In vivo:

Matricaria extracts:
Wound healing activity was determined by Nayak *et al. (2007)* using excision, incision and dead space wound models. Sprague-Dawley rats were divided into two groups of six for each model: animals in the test group were treated with the aqueous extract of *M. recutita* (120 mg/kg/day) (no further specification), which was mixed in their drinking water. Animals in the control group were maintained with plain drinking water. Healing was assessed by the rate of wound contraction, period of epithelialisation, wound-breaking strength, granulation tissue weight and hydoxyproline content on days 1, 5, 10, 15. Wound contraction and epithelisation were significantly better in the test group resulting in a healing 3 days earlier under matricaria, differing from day 10 on. Wound breaking strength in incision wounds was significantly higher in the test group (control 428.30 g ±14.47/ test 654.10±16.50; p= 0.02).

Martins *et al.* (2009) treated 125 wistar rats in 5 groups with: no drugs (group I), Matricaria (commercially in Brazil available matricaria preparation AdMuc; no further specification) (group II), topical triamcinolone acetonide (group III), clobetasole propionate cream (group IV); clobetasole propionate paste (group V). Under anaesthesia traumatic ulcers were applied with an 3 mm circular scalpel. After 1, 3, 5, 7, 14 days each 5 rats were sacrificed to evaluate the grade of wound healing (grade 1 total healing, grade 5 epithelial ulcer and acute inflammatory infiltrate). In the clinical analysis all rats of the matricaria group had healed ulcers at 5 days whereas the other groups reached that status after 14 days. The wound healing in the corticosteroid groups were significantly lower than in the control group. To check the influence of the different tested preparations a viability testing was done with an established cell line of human gingival fibroblasts (FMMI) using MTT reduction. The matricaria replicates (n=8) showed the least viability.

Thirty male Wistar rats (250-300 g) were randomly divided by Jarrahi *et al.* (2008) into three groups, as control, vehicle, and treatment. Second-degree burning was induced in 20% of whole surface area of animal body by placing the back of animal into boiling water for 8 s. Animals of control group received no treatment. Animals of vehicle and treatment groups were treated topically by olive oil and extract dissolved in olive oil (100 g *Matricaria recutita* flowers added to 100 ml olive oil) twice a day respectively from the first day of burn induction to complete wound healing. Control group and vehicle group showed no differences, but the difference between control and verum was statistically significant (p=0.05) and all the wounds were healed 11 days earlier than in the control group.

Assessors comment:
In vivo data of *Matricaria recutita* containing extracts showed in rats a better wound healing than the controls.

Gastrointestinal effects

In vitro:

Matricaria extracts:
Using the isolated guinea pig ileum Forster *et al*. demonstrated the effectiveness of an ethanol extract of matricaria (ratio herbal substance:extraction solvent= 1:3.5; extraction solvent: ethanol 31% (m/m)) on spasms induced by acetylcholine and histamine. At doses of 2.5 and 10 ml/l the matricaria extract increased the median effective dose (DE_{50}) of acetylcholine and histamine in a dose-related

manner, also when the effect of ethanol was subtracted. Nevertheless, the effect was far less than that of the usual therapeutic atropine dose (recalculated to the in vitro system) (Forster *et al.* 1980).

The cyclic nucleotides cAMP and cGMP regulate the smooth muscle tone of the intestinum causing relaxation. Inhibition of phosphodiesterases (PDEs), which catalyse the hydrolysis of cAMP and cGMP to 5'-AMP and 5'-GMP, is one of the mechanisms operated by spasmolytic drugs. The effect of matricaria on cAMP- and cGMP-phosphodiesterases (PDE) was investigated by Maschi *et al.* 2008. Human platelet cAMP-PDE and recombinant PDE5A1 were assayed in the presence of infusions prepared from sifted flowers and capitula. LC-ESI-MS/MS analysis showed different compositions in infusions made with dried flowers (infusion with hot water, lyophilized, DER: 3.5:1). Matricaria inhibited cAMP-PDE activity (IC_{50} = 17.9-27.2 µg/ml), while cGMP-PDE5 was less affected (-15% at 50 µg/ml). Flavonoids showed an inhibitory effect (IC_{50} = 1.3-14.9 µM), contributing to around 39% of the infusion inhibition.

Isolated substances:
The antispasmodic effects of different matricaria compounds have been examined in isolated guinea pig ileum. According to Achterrath-Tuckermann *et al.* (1980) compounds contained in both aqueous and oil extracts of the plant are effective antispasmodics in isolated guinea pig ileum. Compared to papaverine, a smooth muscle relaxing drug α-bisabolol was 91% as effective on spasms induced with barium chloride while bisabolol oxides A and B were 46-50% as effective. Among the flavonoids tested apigenin was 3.3 times more potent than papaverine, followed by quercetin (72% as active), patuletin (68%) and luteolin (44%).

In vivo:

Chamomile extracts:
The effect of ColiMil as phytotherapeutic formulation and its herbal components (methanolic *Matricaria recutita* flowers extract, *aqueous Foeniculum vulgare* fruit extract and aqueous *Melissa officinalis* aerial parts extract) (no further information available) on upper gastrointestinal transit was investigated in mice in vivo. Reference drug was loperamide (~0.25 mg/mous). Oral administration of the herbal formulation (0.4-0.8 ml/mice, corresponding to 0.89-1.78 mg methanolic *Matricaria recutita* extract) dose-dependently delayed upper gastrointestinal transit (lower dosage: 17%; higher dosage: 24%). Matricaria recutita extract itself (0.89 and 1.78 mg/mouse) reduced motility significantly (lower dosage: 10%; higher dosage: 15%). Loperamid reduced motility by 17% (Capasso *et al.* 2007).

Isolated substances:
Apigenin, at 12.5-50 mg/kg administered i.p. reduced both small and large intestinal transit time in mice with castor oil induced diarrhea (Di Carlo *et al.* 1993).

Assessors comment:
Antispamodic effects of extracts and compounds of extracts were described in vitro and in vivo. The clinical relevance of the effects seen in vitro seems to be low, while the effects seen in vivo were seen with a methanolic extract with no further details. A correlation to the extracts/indications of the monograph is not possible, however, a certain plausibility concerning the antispasmodic effects can be retrieved from such data.

3.1.2. Secondary Pharmacodynamics

Antimicrobial activity

Matricaria extracts:
An ethanolic extract of matricaria inhibited the growth of herpes and polio virus (Aggag and Yousef 1972, Vilaginès *et al.* 1985).

In general aqueous extracts of matricaria were more effective against molds and yeast, while alcoholic extracts showed higher activities against bacteria (Al-Ismail and Talal 2003).

Antimicrobial activity of the aqueous extract of *M. recutita* against various microorganisms (*Pseudomonas aeruginosa*, beta haemolytic streptococci, *Enterobacter agglomerans*, *Escherischia coli*, *Staphylococcus aureus*) was assessed. These germs were resistant to the extract (Nayak *et al.* 2007*)*.

Essential oil:
Essential oils extracted from matricaria have exhibited some antimicrobial activity against certain species of bacteria, fungi and viruses in vitro. German matricaria oils were slightly more effective against 25 different gram-positive and gram-negative bacteria and 20 strains of *Listeria monocytogenes* than oil from Roman matricaria (*Chamaemelum nobile*) but neither was as effective as Marrocan Matricaria (*Ormensis multicaulis*) (Lis-Balchin *et al.* 1998). The efficacy of these oils was 8-56%. The antifungal activities of the German matricaria oils against *Aspergillus niger*, *Aspergillus orchraeus* and *Fusarium culmorum* were 63-75% inhibition.

Soliman and Badeaa (2002) reported antifungal activities of *M. chamomilla* oil against *Aspergillus flavus* and *A. parasiticus* as well as F*. moniliforme*. The highest used concentration (3000 ppm) demonstrated the highest inhibition (91-95%).

Effects on the central nervous system

Aqueous extracts of matricaria flowers:
Della Loggia *et al.* (1982) employed a lyophilized aqueous extract of matricaria prepared with 50 g flowers infused for 5 min with 1 l boiling water to study basal motility, exploratory and motor activities of Swiss NOS mice. Long-term motility was reduced by 57.1% within 10 min of treatment with 360 mg/kg matricaria i.p. (n=15) and reached a maximum inhibition of 92.1-97.5%, compared to controls (n=15) 1.5-2.5 h later; motor coordination was not affected. Short-term motor activity was reduced by 90% with a dose of 180 mg/kg i.p. (n=24). Locomotor activity was reduced by 46.0% and 56.5% and the number of head-dippings reduced by 34.4% and 39.4% with doses of 180-320 mg/kg i.p. respectively. Matricaria administered at 160 and 320 mg/kg i.p. (n=16/group) potentiated hexobarbital-induced sleep in mice by 37.1% and 62.7% respectively, compared to controls given 100 mg/kg of the barbiturate alone.

Shinomyia *et al.* (2005) observed that a matricaria extract, prepared by refluxing water in 1 h, has benzodiazepine-like hypnotic activity to be antagonized by flumazenil, a BDZ receptor antagonist, at a dose of 3 mg/kg. The substance showed a significant antagonistic effect on the shortening in sleep latency induced by matricaria extract at a dose of 300 mg/kg. No significant effects were observed with the matricaria containing extract on total times of wakefulness, non-rapid eye movement (non-REM) sleep and REM sleep.

Essential oil:
In a study of ovarectomized rats Yamada *et al.* (1996) found that inhaling the vapour of matricaria oil reduced a stress-induced increase in plasma adrenocorticotropic hormone (ACTH) levels. Diazepam co-administered with the matricaria oil vapour, further reduced ACTH levels , while flumazenil, a benzodiazepine (BDZ) receptor antagonist blocked the effect of matricaria oil vapour on ACTH.

Isolated substances:
Viola *et al.* (1995) tested a purified fraction of an aqueous matricaria extract containing apigenin administered i.p. to examine its effects on anxiolytic, sedative, locomotor, myorelaxant and anticonvulsive activities in mice. At 3 mg/kg, a dose similar to those used for benzodiazepines, apigenin significantly increased the percentage of entries and time spent in the open arms of an elevated plus maze, behaviors indicative of an anxiolytic effect. Doses up to 10 mg/kg produced no

changes in spontaneous ambulatory locomotor activity: at 30 and 100 mg/kg there was a 26% and 46% reduction in activity, respectively, and a moderate decrease in the head-dipping behaviors indicating a mild sedative effect. At 100 mg/kg apigenin had no myorelaxant effect, in contrast to 3 mg/kg diazepam. In mice treated with doses up to 80 mg/kg apigenin no significant anticonvulsant activity was found after challenge with 50-80 mg/kg of the seizure inducing pentylneterazole; however at 20, 40, 80 mg/kg apigenin increased the onset time of convulsions by approximately 2 fold compared to controls.

Avallone *et al.* (2000) tested much lower doses (0.5-10 mg/kg apigenin) without being able to show an anxiolytic effect. At 1 mg/kg the number of entries and time spent in the open arms of an elevated plus maze were higher than the control group, but did not reach statistical significance. The authors reported similarly that apigenin had no myorelaxant effect up to 50 mg/kg and no effect on picrotoxin (6-8 mg/kg) induced convulsions at 25 and 50 mg/kg apigenin. But apigenin reduced significantly the time of latency in the onset of convulsions. Open filed tests showed significant reductions in locomotor activities compared with controls at apigenin doses of 25 and 50 mg/kg but not at 12.5 mg/kg indicating a sedative effect at higher doses similar to Viola *et al.* (1995). The lack of effect with the addition of a benzodiazepine agonist to apigenin treated animals suggests that the sedative properties of apigenin may not be due to a direct effect on benzodiazepine receptors, but to other neurotransmitters.

Salgueiro *et al.* (1997) observed that 10 mg/kg apigenin administered to Wistar rats either pre- or post-training had no effect on training or test session performance of inhibitory avoidance , active avoidance or habituation to an open field , unlike diazepam which had an amnestic effect on animals subjected to the same tests. Also in contrast to diazepam, apigenin had no effect on the tail-flick test, indicating the lack of an analgesic effect. These results also suggest that apigenin affects benzodiazepine receptors differently than classical benzodiazepine receptor ligands such as diazepam.

According to Medina *et al.* (1998) the separation index (ratio between the maximal anxiolytic dose and the minimal sedative dose) for diazepam is 3 while for apigenin is 10. Compounds, other than apigenin, present in extracts of matricaria can also bind benzodiazepine and GABA receptors in the brain and are thought to be responsible for some of the sedative effects; however many of these compounds are unidentified (Avallone *et al.* 1996).

3.1.3. Safety Pharmacology

No information available

3.1.4. Pharmakodynamic Interactions

No information available

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

3.2.1. Absorption, Distribution, Metabolism, Elimination

There are no data available.

3.2.2. Pharmokokinetic interactions

In vitro data:

Matricaria extracts:
Human CYP 450 3A4 was inhibited 50% (IC_{50}) with a commercially available ethanol extract of matricaria diluted to 1-2% of full strength, not corresponding to the monograph (Budzinski *et al.* 2000).Whether these data are transferable to matricaria tea has yet to be determined (see case B Nowack *et al.* 2005*).*

Essential oil:
Ganzera *et al.* (2006) published an in vitro study on the inhibitory effects of the essential oil of matricaria and its major constituents on human cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6, CYP3A4). Crude essential oil (characterized via GC separation) demonstrated inhibition predominantly on CYP1A2 (IC_{50}=1.59 µg/ml) followed by CYP3A4 (IC_{50}=4.97 µg/ml). Chamazulene (IC_{50}=4.41 µM), *cis*-spiroether (IC_{50}=2.01 µM), *trans*-spiroether (IC_{50}=0.47 µM) were potent inhibitors of CYP1A2, being also active on CYP3A4. CYP2C9 and CYP2D6 were less affected.

In vivo data:

Matricaria extracts:
Maliakal and Wanwimolruk (2001) reported on the effects of herbal teas on hepatic drug metabolizing enzymes in rats. 6 groups of 5 female Wistar rats each had free access to peppermint, dandelion and matricaria tea (2% w/v of dried flower heads of *Matricaria recutita*), water as control, green tea extract (0.1%) and aqueous caffeine solution (0.0625%). After 4 weeks of pretreatment different cytochrome isoforms and phase II enzyme activities (UDP-glucuronosyl transferase and glutathione-S-transferase) were tested with appropriate substrates (phenacetin 5 µM for CYP1A2). Activity of CYP1A2 in the liver microsomes of rats was significantly decreased to 39% of the control (p=<0.05) by matricaria tea.

Assessors comment:
From preclinical data in rats an interaction of matricaria containing products resulting in a reduction of CYP 1A2 in rats must be taken into account.

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

Single/repeat dose toxicity:
No data available.

Genotoxicity studies:

Matricaria extracts:
Kalantari *et al.* (2009) studied an matricaria containing preparation (no further details available) from Iran in a the short-term mouse peripheral blood micronucleus test. Doses of 2.5, 5 and 10 ml/kg were used for test groups. Drugs were administered twice in 24 h intervals. Blood samples were prepared 48 h after first administration of drugs and kept on precoated Acridine orange slides. The scoring of micronucleated reticulocytes were carried out per 2,000 counted reticulocytes in each slide by fluorescent microscope. For matricaria the micronuclei increased from 2 to 4.5 without informations on mean and variance. The test is not guideline conform due to the lacking second point of measurement.

Romero-Jiménez et al. (2005) tested *Matricaria recutita* using one tea bag of a local health store in 200 ml of water (no further details available).The Somatic Mutation And Recombination Test (SMART)

in *Drosophila melanogaster* was performed. The infusion in all strengths showed no significant genotoxicity in all strengths.

Isolated substances:
Anter *et al.* (2011) evaluated the genotoxic, antigenotoxic, tumoricidal, and apoptotic effect of some major phenols (apigenin, bisabolol, and protocatechuic acid) from two medicinal plants, *Matricaria chamomilla* and *Uncaria tomentosa*. The wing spot test of *Drosophila melanogaster* was used to evaluate the genotoxicity and antigenotoxicity of the three phenols. The human model of HL-60 leukemia cells was used for the assessment of the cytotoxic effect, growth, and cellular viability. The apoptotic effect was evaluated using a DNA fragmentation assay based on the formation of internucleosomal units. Protocatechuic acid (0.25 and 1 mM), apigenin (0.46 and 1.85 mM), and bisabolol (0.56 and 2.24 mM) did not exhibit any genotoxic effect.

Gomes-Carneiro *et al.* (2005) tested the mutagenic activities of α-bisabolol in the Salmonella/microsome assay. Mutagenicity of α-bisabolol was evaluated with TA100, TA98, TA97a and TA1535 *Salmonella typhimurium* strains (50 and 150 µg/plate), without and with addition of S9 mixture. No increase in the number of his^+ revertant colonies over the negative (solvent) control values was observed with any of the four tester strains.

Assessors comment:
The tests on genotoxicity which are published cannot be used to assess the genotoxic potential of the preparations covered by the monograph. The micronucleus test performed by Kalantari *et al.* cannot be transferred to any of the preparations of the monograph due to a lack of description of the preparation tested. Furthermore it is to point out that authors themselves classified the preparation as equivocal genotoxic (it is to note, that the test was not guideline conform, e.g. due to a lacking second measurement point). All the other tests were done with isolated substances or with test systems regulatory not accepted.

Carcinogenicity, reproductive and developmental toxicity and local tolerance:
No data available.

3.4. Overall conclusions on non-clinical data

Many pharmacological studies have demonstrated that Matricaria preparations and their constituents display many properties in vivo and in vitro. A systematic review of all these studies was not possible due to the huge amount of published data. Emphasis was put on studies with relevance for the clinical usage. The non-clinical data support the traditional use. Anti-inflammatory effects and effects on wound healing and on gastrointestinal tract were seen in vivo. Unfortunately, most of the studies do not provide exact extract specifications or dosages/concentrations.

Data on pharmacokinetics are limited. From in vitro and in vivo data influence on CYP1A2 seems to be at least conceivable. Further monitoring is necessary in order to draw conclusions on the clinical relevance of these findings.

Non-clinical information on the safety of matricaria preparations is scarce. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

4. Clinical Data

4.1. Clinical Pharmacology

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

Cutaneous use:

Pharmakodynamic data exist mainly for the cutaneous use.

The antiphlogistic effect of n) liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) was tested compared to the cream basis of Kamillosan and hydrocortisone containing cream using reflexphotometry (Wells Test). 6 healthy male and female probands. A tesafilm stripping and the identification of treatment areas at the back were used. Every hour for 8 h 10 control points /area were checked. The evaluation was a optic one following a 4 point Likert scale (1 = no healing; 2 = slight healing; 3 = good healing; 4 = complete healing). The AUC´s (area under curve) were compared. Kamillosan cream showed a slightly better effect than the basiscream, the low hydrocortisone concentration of 0,25% showed an overall minor effect (Albring *et al*. 1983).

After application of a solution of 15% sodium lauryl sulphate for 120 min the skin of 20 healthy adults (28-42 years, male and female) was washed with water and air dried. For 4 days the relevant ointment (extract o); base; 0.1% hydrocortisone acetate in base of extract o) containing product) were administered 2-3 times a day. 2 h thereafter the skin profile was measured. Baseline measurement was done every 2 days 3 times on the untreated skin. The study demonstrates the antiphlogistic effect of matricaria in a detergent damage of the skin (Nissen 1988).

Kerscher irradiated the skin of 24 probands (age 23-35; 11 m, 14 f) on their back in 8 areas with a Waldmann UV 800 lamp with 20-160 mJ/cm^2. Thereafter liposome preparations of Matricariae flos extract 10%, base, liposomal gel preparation of matricaria flos (2%), base, Matricariae flos containing cream, base, hydrocortisone 1% ointment; hydrocortisone 0.5% ointment were applied for 2 days. The assessment of the redness was done with a Minolta Chromometer CR 200 on a Likert Scale (0=strong; 1=weak; 2=no effect). The resulting anti-inflammatory effect was strongest under hydrocortisone 1% (100%); Kamillosan cream (72%) base 50%.

Korting *et al*. (1993) showed anti-inflammatory effects of a matricaria containing cream (20 mg/g extract n) cream) in compared to 1% hydrocortisone cream and to 2 different amounts of hamamelis containing crème in UV erythema tests (24 probands) und cellophane tape stripping tests at the back skin of 24 healthy probands compared to suitable bases measured by visual score and chromometry, The antiphlogistic effect of the matricaria containing preparation was a little less than the lower hamamelis dose and both less than 1% hydrocortisone. 12 probands were in the matricaria group; 5 point Likert scale from very intense redness (0), to intense erythema (1), to moderate erythema (2), faint residual erythema (3) to no erythema. A noteworthy difference to control was in the visual scores for matricaria cream (P=0.0625) at 4 h.

Assessors comment:
The human pharmacological data cover the cutaneous use and support the plausibility of the anti-inflammatory effects of the relevant extracts.

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

4.2. Clinical Efficacy

4.2.1. Dose response studies

See 4.2.2 Generalized Anxiety Disorder (Amsterdam *et al.* 2009), which is an exploratory dose escalation study. Classical dose response studies are publically not available.

4.2.2. Clinical studies (case studies and clinical trials)

Internal use

Oromucosal use:

Nasemann treated 29 outpatients and 49 inpatients with different oral diseases (mouth ulcers n=19; lingua geographica n=4; Lichen ruber mucosae n=4; contact dermatitis etc.) with rinsing 6 times per day with m) liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) applying 15-20 drops/glass of warm water in an open uncontrolled trial partly cross over with warm water or sodium chloride solution. All patients had a cooling effect and a sustainable effect regarding the diminished foetor ex ore and a reduction of pain if they suffered from mouth ulcers. The study supports the antiphlogistic effects of Kamillosan concentrate rinsing, but due to lacking controls does not support the well-established use. Traditional use is covered for oromucosal use (Nasemann and Menzel 1975b).

Carl tested Liquid extract m) (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) in an uncontrolled prospective study in 98 patients under radiation (n=20; head and neck tumors) and 78 patients receiving different polychemotherapies (n=46 prophylactic; 32 with established mucositis. Regarding the prophylactic use under polychemotherapy 78% of the patients did not develop a mucositis. Therapeutically the patients were after 3 days better, free of complaints. Under radiation 1/20 developed a grade 3 mucositis; 13/20 grade 2 6/20 a grade 1mucositis. The study gives strong hints to a prophylactic efficacy of Kamillosan concentrate rinsing under polychemotherapy, but is not reliable due to lacking controls. The study is irrelevant for the traditional use because the indication is irrelevant. An antiphlogistic effect of Matricariae flos in oromucosal use is supported (Carl and Emrich 1991).

In a double blind placebocontrolled prospective clinical study with two arms Fidler reported about the prophylactic use of liquid extract m) (1:4.0-4.5) from matricaria flos extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) applying 30 drops in 100 ml warm water 3 x/d after a cooling of the mouth (icelozenges) for 30 min before polychemotherapy as an add-on. 164 patients receiving the first cycle of a 5 fluorouracil containing polychemotherapy sucked ice cubes for 30 min. The study showed no difference between verum and placebo. The study is possibly negative due to the extreme cooling measures before therapy. It does not support the efficacy regarding the well established use. The study is irrelevant for the traditional use because the indication is irrelevant. An antiphlogistic effect of Matricariae flos in oromucosal use is supported (Fidler *et al*. 1996).

Inhalation:

In an open uncontrolled study Troll (1990) reported of 47 patients with different inflammatory diseases of the sinusitis, pharyngitis, tonsillitis using either liquid extract m) (1:4.0-4.5) from matricaria flos

extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) or an ethanolic extract from matricariae flos (liquid extract m) 370.5 mg, peppermint oil 18.5 mg, anise oil 7.0 mg. Duration of treatment was 6-9 days. 88-100% of patients felt better. No further criteria documented. The study documents the use of the inhalation and the use as mouth spray, but is not sufficient to support the efficacy according to well established use of the used preparations.

In an open uncontrolled study 53 patients with sinusitis maxillaris received an operative (n=34 tamponade) or conservative treatment (n=19 irrigation). Steam inhalations were done 2 x/day with 20 ml/1 l hot water m) liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide). At the end of therapy the quality of secretion (none/watery/bloody/ watery-bloody) was documented. Pain was documented (4 point Likert scale) and tolerance were documented. The study documents the use as inhalation but does not support efficacy for well established use, due to lacking controls (Sauer 1990).

Oral use

Gastrointestinal complaints:

In an uncontrolled multicentre study 104 ambulant patients with unspecific gastrointestinal complaints (pressure in the stomach; eructation, heartburn; loss of appetite; nausea; vomiting) were treated for 6 weeks with 4 times/d 25 drops of liquid extract m) (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide). 44.2% of the patients were without complaints. Pressure in the stomach was better in 84.5%; eructation in 77.5%, heartburn in 81.7%; loss of appetite in 61%; nausea in 88.7%; vomiting in 77.8% (Stiegelmeyer 1978).

Assessors comment:
Due to lacking controls the study does not support efficacy regarding well-established use but can be used to support traditional use in gastrointestinal complaints (indication1).

Dysmenorrhoea:

In Madaus (1979) there is a recommendation to treat dysmenorrhea with a combination herbal tea of Valerianae radix, Menthae piperitae folium and Matricariae flos. Madaus does not separate homeopathic use from herbal use.

Wichtl (2002) and Wagner (1995) do not mention the internal use of matricaria containing herbal medicinal products in dysmenorrhea.

The ESCOP monograph (2003) and the WHO monograph (1999) regarding *Matricaria recutita* does not cover the internal use in dysmenorhoea.

Le Cahiers de l´Agence Nr.3 Médicament à base de plantes (1998) does not mention a traditional use for matricaria flos containing herbal medicinal products in dysmenorrhea. The entry covers “camomille grande (aerial parts)” for painful periods.

Assessors comment:
Because of lacking literature regarding the tradition of the internal use of matricaria containing herbal medicinal products in dysmenorrhea the indication cannot be supported for the monograph unless further information is added.

Generalized Anxiety disorder (GAD):

In a randomized, double-blind, placebo-controlled GCP conform clinical trial in parallel groups 61 patients were enrolled fulfilling the following criteria: adult patients, Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) Axis 1 diagnosis of GAD ascertained through Structured clinical Interviewfor DSM IV interview format, HAM-A Baseline ≥9, other comorbid DSM IV Axis 1 Disorders were not excluded, if they were independent (Amsterdam *et al.* 2009). Women of childbearing potential used a medically proven contraception and had to deliver a negative pregnancy test before the study. Major depressive disorders; bipolar disorder, panic disorder, phobic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, substance-induced anxiety disorder, psychosis, dementia, substance abuse or dependence during the preceding 3 months, unstable medical condition, hepatic or renal insufficiency, malignancy, abnormal serum thyrotropin level of ≥5 µlU/ml, known sensitivity to *M. recutita* or other asteraceae; concomitant medication with anxiolytics, antidepressants, mood stabilizer, sedatives, or CAM remedies (e.g.: Hypericum) or other matricaria preparations were excluded. 4 patients dropped out due to screen failure (3 withdrawn consent, 1 noncompliant). After randomization 28 patients received: matricaria extract standardized to a content of 1.2% apigenin (Spectrum Pharmacy Products New Brunswick NJ); 1 capsule containing 220 mg Matricaria extract (no extract specification).

Aroma blinding by a disk of 1 %matricaria oil or neutral oil to the lid of each airtight medication container.

Posology: 1. week: 1 cap per day

2. week: 2 caps per day

For patients with a reduction of HAM-A Score ≥ 50%/baseline:

3. week: 3 caps per day

4. week: 4 caps per day

For patients continuing to have a ≥50%/baseline reduction weeks 5-8 were treated with 5 caps/d.

The detectable effect size was 0.57 with 80% power (0.68/90%) primary comparisons implemented quasi least squares with 2-sided tests of hypotheses and P=0.05 as criterion for statistical significance using Stata 10.0. The use of Markov correlation structure (models the correlation between repeated measures and is appropriate for unequal measurement times).

Regression models were used to test the primary hypotheses. Last oberservation carried forward (LOCF) analysis to examine change in total HAM-A Score between treatment conditions. X2 test was used to compare the proportion of responders (with 50% reduction or more in baseline HAM-A Score) ITT approach handles drop outs as non-responders. Wilcoxon rank sum test (differences in the demographic Fischer exact test (frequencies of adverse events) t-Test (incidence rates data and of adverse events in escalating doses)

The reduction of HAM-A Score: matricaria vs. placebo 60β3:= -3.17; 95% CI-6.29 to -0.45; P=0.047; the secondary outcomes are without a significant result. An influence of the taken doses to responder or non-responders could not be shown. The adverse events were more common in placebo (22) than in verum (11) without clear specification. Higher matricaria doses did not increase the rate of AE.

Assessors comment:

The small study of very good quality with an dose escalating design shows a statistically significant clinically relevant reduction of HAM-A Score in mild to moderate general anxiety disorder. Including an

indication as GAD into the WEU part of the monograph will not be possible, since the indication does not fulfil the WEU criteria and the tested pharmaceutical preparation is neither specified nor fulfils the European Market presence. Additionally it is a small exploratory study with dose escalation, larger studies are needed. Traditionally it may not be used due to the short time frame since publication.

Cutaneous use

Atopic dermatitis/eczema:

Nasemann reported in his abovementioned study the use of a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m) in 7 patients suffering from dermatitis hypostatica with contact senzitation. This supports the traditional cutaneous use (Nasemann and Menzel 1975b).

161 eczema patients were treated acutely with diflucortolonvalerat 3-14 days. When only an erythema with a slight infiltrate were seen, the left side was treated with a liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= liquid extract n). The right side was treated with either 0.25% hydrcortisone, 0.75% fluocortinbutylester cream or with 5% Bufexamac (cream). In the evaluation extract n) was estimated as good as 0.25% dydrocortisone, better than fluocortinbutylester and considerably better than Bufexamac. The study does not support efficacy according to well-established use, but documents the traditional use cutaneoulsly. Data regarding safety are lacking. The study documents the traditional use for cutaneous administration, but does not support WEU (Aertgeerts 1985).

In a blind, placebo controlled randomized, monocentric study comparing both sides 72 patients suffering from a moderate atopic dermatitis of both arms received 2 times per day

- Matricariae flos vs. hydrocortisone
- Matricariae flos vs. placebo cream
- hydrocortisone vs. Matricariae flos
- placebo cream vs. Matricariae flos

The study showed a tendency of extract n) containing cream to be superior to hydrocortisone cream, but no superiority against placebo. The study is not suitable to support WEU but covers traditional use on the skin in moderate atopic dermatitis (Patzelt-Wenczler and Ponce-Pöschl 2005).

Radiation skin reaction in breast cancer patients:

The efficacy of a liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= liquid extract n) versus almond ointment was tested on acute radiation skin reaction in 50 female patients with breast cancer after operation during irradiation (5 times a week 2 Gy). The irradiated area was between 10 to 10 and 17 to 17 cm. 30 min before irradiation and at bed time the randomized preparation was applicated one above and one below the scar. The evaluation took place after 10 Gy and 2 weeks/3 months after the irradiation according to a 4 point Likert scale (0= unchanged; 1=slight reddening; 2= explicit redness; moistening dermatitis) Under Kamillosan the grade 1 reaction occurred slightly later and grade 2 reactions were 7/13 under almond ointment. The study is too small to support WEU, the indication is not apt to be treated traditionally, but the study support s a moderate antiinflammatory effect of Kamillosan cream (Maiche *et al.* 1991).

Wound healing after proctologic operations:

Marti (1977) documented the results of Kamillosan hip baths after sphincterektomy due to anal fissures in 50 patients. The wound healing was normal. No safety concerns were reported.

Assessor´s comment:

These data have observational quality and support the plausibility of the traditional use as hip baths.

50 patients (28 m; 22 w) suffered from different proctologic diseases (fistulae; perianal thrombosis; marisca) were postoperatively divided in two groups. All received 3 x/d a hip bath with a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m). One group received additionally gauze compresses with a liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) the other with dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide). A quick wound healing was observed without any differences between the groups. The study is not suitable for a efficacy assessment according to WEU criteria due to lacking controls, but does support the traditional use in wound healing of superficial wounds (Förster 1987).

Decubital ulcer/Ulcera crurum:

182 patients, 123 thereof with ulcera crurum (86 f, 37 m,), 35 with decubital ulcers (16 f, 19 m,), 24 toddlers with diaper rash (11 f, 13 m,)(see children assessment) were treated with a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m) and additionally with dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= dry extract o), if infected. Clean ulcera crurum were treated extract o). Ulcers with necroses, scabs or superinfection received dressings with extract m)several times a day and a extract (o) for the night. Therapeutic success (very good or good) in decubital ulcers 60%, ulcera crurum 83% (Aertgeerts 1984).

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

General:

Jeschke *et al.(*2009) reported about the risks of asteraceae containing extracts in german primary care. 362 physicians were contacted to participate in an online system to document all prescriptions of asteraceae containing extracts with the corresponding adverse drug reactions (ADR). 107 physicians agreed to participate. 38 fulfilled the technical requirements. 55% were general practicioners, 45% specialists (23%pediatricians, 11% internal medicine, 11% others). From September 2004 - September 2006 50,115 patients were documented. Who received 1,999,387 prescriptions for 360,488 drugs. 18,830 Patients received 25,652 prescriptions with 42,378 remedies containing herbal substances or herbal preparations from plant species of the asteraceae family. ADRs were evaluated according to WHO Adverse reaction terminology. The statistical analysis showed that in children the asteraceae containing drugs were prescribed regularly (60%). The most frequently prescribed species was *Matricaria recutita* (49.9% of adult male, 32.3% of female adult, 51.7% in children). *Matricaria recutita* was predominantly prescribed as herbal monopreparation (75%). It was used for diseases of the middle ear (10.3%), oral cavity and jaws (8.3%), salivary glands, infectious diseases especially for the upper respiratory tract (16.2%) ADR´s related to *Matricaria recutita* were rare. For the entire sample of 18830 patients no serious ADR was reported. In the analysis of the subgroup of seven physicians who also documented non serious ADR´s, 11 non serious ADR´s for Asteraceae containing remedies occurred in 6961 patients. 2 of these ADR´s were connected to preparations containing Matricaria flos. 1 case was a mild allergic reaction of the skin after oral administration of a combination

product containing *Artemisia abrotanum and Matricaria recutita* to a female 71 year old with an acute gastroenteritis. The second case was a gastralgia during a acute gastroenteritis of a 47 year male adult, which was classified as possible, but could as well be connected to the underlying disease. The incidence was 2/1602 patients receiving matricaria containing preparations (0.12%).

Internal use:

The available studies regarding children in internal use are done with different combination products, as

herbal tea (matricaria, vervain, licorice, fennel, balmmint)

standardized extract of matricaria (*M. recutita*), fennel (*Foeniculum vulgare*), and lemon balm (*Melissa officinalis*)

liquid preparation containing apple pectin and matricaria fluid extract standardized to 2.5 g chamazulene/100 g

and are to be used to assess the safety of matricaria containing products in children but may not be used to assess efficacy. There are no clinical studies available concerning the internal use either as inhalation o as oral administration in children.

Cutaneous use:

Aertgeerts (1984) reported on an oberservational study which included 182 patients who were treated with Kamillosan ointment (extract m)), 2 to 3 times daily, thin layer; fluid, 15 ml/l water for compresses, 5 to 7 ml/l for bath preparation and 15 ml/l water for washings). 24 infants (average age 7.5 month) were treated for diaper dermatitis, 123 were treated for ulcus cruris and 35 patients were treated for ulcus decubitus. Duration of treatment was varying. Although the design of the study was not suitable for substantial conclusions on efficacy – beside a general tendency on a positive effect – it is remarkable that especially the treatment of infants did only show irritation in two cases possibly due to occlusive conditions. For 22 infants no side effects were observed.

Remme and de Witt (1984) studied the efficacy of liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m)) and a dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= dry extract o)) in 54 patients with ulcera crurum. 17 of them suffered from an accompanying eczema. The evaluation followed the survey of the wounds (2 x/week); status documentation (healed, better, unchanged; worsening). The eczema was monitored in $cm^{2,}$ status documentation (healed, better, unchanged; worsening). At the end of treatment there was a global assessment of efficacy (good, sufficient, minor, no) The patients received 4% extract m) as compresses changed 4 times daily or 1 x extract o). 5 patients dropped out due to superinfection, 7 patients were healed, 41 better, 4 unchanged, 2 worsened.

Peters (1987) observed the efficacy of a basis diet with a cortisone free local treatment matricaria flos containing ointment. These observational data are too poorly documented to support efficacy, but document the traditional use.

In an open controlled study with 55 children the efficacy of extract n) in treatment of diaper dermatitis was investigated (Viegas *et al*. 1996). Extract n) cream was applied with every change of diapers, duration of use was two weeks. The result of treatment was analysed by means of a 4-point-score. Symptoms improved after 7 days and recovery was nearly complete after 14 days. The study is

suitable to demonstrate the cutaneous medicinal use of extract n) cream in children from 2 weeks to 3 years of age.

Stechele (1991) treated 76 infants and toddlers (2/3 in between 1 and 10 months) in several indications (diaper dermatitis, seborrhoic eczema and peroral eczema) with extract n) cream three times daily over 8 days. There were no adverse effects observed. The study does not allow any conclusion towards efficacy due to lacking controls.

Assessors comment:

According to the traditional data and the cited studies the following preparations can be accepted in pediatric use with posologies:

comminuted herbal substance a)

Indication1)

Oral use: children from 6 months – 12 years

4.3. Overall conclusions on clinical pharmacology and efficacy

The Matricaria containing preparations included in both monographs have been used in Europe for more than 30 years. Besides a lot of traditional literature regarding this use, which is not unrolled here enough senior studies are available to support the plausibility of the traditional use in the cited indications of the monograph.

Indication 1) **Traditional herbal medicinal product used for the symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms** is supported by an uncontrolled multicentre study on 104 patients published 1978, which is covering thirty years of use in the EU for of extract m). Due to lacking controls the study does not support efficacy regarding well-established use but can be used to support traditional use in the indicated posology for adults in gastrointestinal complaints (Stiegelmeyer 1978).

Indication 2) **Traditional herbal medicinal product used for the relief of symptoms of common cold** is supported by the clinical studies (Schmidt 1975) (Lauber 1987) being made to assess local tolerance of inhalation support the traditional inhalative use (see 5. Clinical safety). The open uncontrolled study of Troll (1990) tested steam inhalation versus mouthspray and is supporting the traditional use of steam inhalation. The observational study of Sauer (1990) supports this use as well for ethanolic extracts in inhalation in the specified posologies for ethanolic extracts.

Indication 3) **Traditional herbal medicinal product for the treatment of minor ulcers and inflammations of the mouth and throat.** The traditional oromucosal use is supported by open clinical studies by Nasemann (1975a), Carl (1991) and Fidler (1996) in the specified posology.

Indication 4) **Traditional herbal medicinal product used for adjuvant therapy of irritations of skin and mucosae in the anal and genital region, after serious conditions have been excluded by a medical doctor.** is supported by an open clinical study (Förster 1987a) supporting the use of ethanolic extracts as hip bath after haemorrhoids ligature. In another clinical study Foerster explored the different uses as hip bath, cream and ointment after different anal diseases: perianal thrombosis, mariscs and anal fistulae (Foerster 1987b).

Indication 5) **Traditional herbal medicinal product used for the treatment of minor superficial wounds and small boils (furuncles)** is supported by open clinical studies (Aertgeerts 1984, Förster 1987). These studies are not apt to support WEU, due to lacking controls but cover the traditional plausibility in the relevant posologies.

4.4. Overview of toxicological/safety data from clinical trials in humans

Inhalation:

Bronchial hyper-reagibility/obstructive lung disease

Lauber reported about the treatment of 12 patients with unspecific bronchial hyper-reagibility and 22 patients with obstructive lung disease under bronchiospasmolytic therapy, who received 10 min of steam inhalations (10 ml liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m)) in 450 ml boiled water/10 ml substitute in 450 ml boiled water for two consecutive days. Before and after the steam inhalation body plethysmography and spirometry were tested. No diminishing effects could be documented (Lauber 1987).

Chronic obstructive lung disease (COPD):

10 patients suffering from COPD and 15 healthy probands were treated via inhalation with a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m) in a dilution 1:10 for 10 days. Before and 30 min after the steam inhalation vital capacitiy and one second capacity (FECV) were tested with a body plethysmograph once a day for 10 days and 7 days later. No significant decrease of bronchial resistance was observed. No adverse effects were observed (Schmidt 1975).

Cross-reactivity with other species of the Asteraceae:

24 adult patients (14 f, 10 m) with asthma and rhino-conjunctivitis primarily sensitised to Artemisia vulgaris on the Canary Islands were skin tested with a battery of common inhalant antigens and to foods of vegetable origin. Bronchial tests were conducted following a standardized protocol using the same lyophilized and reconstituted extracts of A*rtemisia vulgaris* (plant part not specified) and *M. chamomilla* (the extract specifications are lacking). The test was stopped when a fall in the FEV_1 (Forced Expiratory Volume in 1 second) of 20% was reached. The conjunctival test was stopped, when a reaction at the eye was seen in absence of a reaction of the contralateral eye. The oral provocation was performed with matricaria tea ingesting 10 ml the patient stopped when symptoms started or after 200 ml of tea ingestion. All patients had a positive skin test to *A. vulgaris*; 21 were positive *M. chamomilla*, 11 patients were positive to other common inhalative antigens, 9 were positive to other food antigens and 17 reacted to pollen of other asteraceae. In the conjunctival test 18 were positive to *A. vulgaris*, 13 to *M. chamomilla*. 15 were positive in the bronchial test to *A.vulgaris*, 16 to *M. chamomilla*. In the oral provocation 13 patients reacted with mild perioral allergy symptoms (pruritus, angioedema of the lips) (de la Torre Morin 2001)

Assessors comment:

Crossreactivity to other asteraceae is covered by the monograph.

Fourteen patients with a history of allergy either to matricaria or to spices or weeds, and a positive skin prick test/RAST to matricaria were investigated by Reider *et al.* (2000) for related allergic reactions to food, pollen and others. IgE-binding patterns were determined by immunoblotting, inhibition tests and deglycosylation experiments. Ten of 14 patients had a clinical history of immediate-type reactions to matricaria, in some cases life threatening. Concurrent sensitization to mugwort and birch pollen is not infrequent.

Hausen (1996) published data from allergy testing with a Compositae plant mixture. One hundred eighteen of 3,851 tested individuals gave a positive response (3.1%). Further tests with the single species of the mixture revealed a high percentage of reactions to feverfew (70.1%) and lower responses to chrysanthemums (63.6%), tansy (60.8%), matricaria (56.5%), arnica (51.8%), yarrow (51.8%).

Paulsen (2002) resumes in her review regarding contact sensitization from compositae containing herbal remedies, that there is no difference between the different preparations of *Matricaria recutita* and that the sensitization/elicitation risk for dermatitis is low.

Cutaneous use:

Aertgeerts published, that from 123 patients with ulcera crurum, treated with a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) and a dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide), dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= dry extract o)), 5 developed an eczema, which represents the risk of senzitation in cases of chronic wounds from externa. Due to the observational quality of data, the differentiation between Matricaria flos and base components is not carried out. The described macerations (4 in decubitus and 3 in ulcera crurum) are probably due to the wound management and not matricaria specific (Aertgeerts 1984).

Remme and de Witt (1984) studied the efficacy of Liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m)) and a dry extract (11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= dry extract o)) in 54 patients with ulcera crurum. 17 of them suffered from an accompanying eczema. The evaluation followed the survey of the wounds (2 times/week); status documentation (healed, better, unchanged; worsening). The eczema was monitored in $cm^{2,}$ status documentation (healed, better, unchanged; worsening). At the end of treatment there was a global assessment of efficacy(good, sufficient, minor, no) The patients received 4% Kamilllosan concentrate as compresses changed 4 x daily or 1 x Kamillosan ointment. 5 patients dropped out due to superinfection, 7 patients were healed, 41 better, 4 unchanged, 2worsened.1 contact allergy was reported. A differentiation which allergen was responsible was not performed.

In an open uncontrolled trial 512 patients suffering from contact eczema received an epicutaneous test with a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m)) in a concentration of 0.5%.The evaluation followed 48 and 96 h thereafter. 28 received the same test with undiluted extract m). Just one patient with a known allergy to matricaria even when she collected them reacted with a type IV allergy to undiluted extract m), but not towards diluted extract m). The study cannot be used to assess a senzitisation potential, because the prophetic testing is lacking, but supports a low allergic risk of matricaria flos during traditional use (Jablonska and Rudzki 1996).

Rudzki and Jablonska (2000) published a parallel design with 982 outpatients with known type IV sensitising, of whom 830 received a patch test with 18 contact allergens as well as a liquid extract (1:4.0-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract m)) in a concentration of 0.5%, respectively a liquid extract (2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= liquid extract n)) or a dry extract (= extract o))(applied as ointment). One patient reacted with a type IV allergy, one with a known type 1 allergy

did not react with atype IV pattern. The study cannot be used to assess a senzitisation potential, but supports a low allergic risk of matricaria flos during traditional use.

Paulsen *et al.* (2008) tested 8 of 12 matricaria-sensitive patients positive to matricaria-containing preparations, including tea, creams, ointments, and oil. 5 of 6 arnica-sensitive persons tested positive to arnica-based products. Compositae-allergic persons should be warned against topical use of Compositae-containing products.

20 patients with a known contact allergy to sesquiterpene lactones (SLs) were recalled by Lundh *et al.* (2006) and patch tested with aqueous extracts of 8 different herbal teas based on Asteraceae plants as well as with parthenolide and other SLs. In 18 of 20 patients with SL allergy, there were positive test reactions to the Asteraceae teas, mainly to those based on matricaria, dandelion and wormwood.

Tea made from matricaria flower was separated by thin-layer chromatography by Lundh *et al*. (2007). Strips of the thin-layer chromatograms were used for patch testing SL-positive patients. 15 (43%) of 35 patients tested positively to 1 or more spots on the thin-layer chromatogram, with many individual reaction patterns.

4.5. Patient exposure

The following table gives an overview of available data on adults, children and pregnant women treated with *Matricaria recutita* containing products.

Publication	**cutaneaous use n=persons**	**Internal use n=persons**	**Inhalation n=persons**	**Gargling/rinsing n=persons**
Adults				
Aertgeerts *et al*. 1984	158			
Aertgeerts 1985	161			
Amsterdam 2009		28 GAD US		
Carl 1991				98
Fidler 1996				81s
Foerster 1987	50			
Jablonska and Rudzki 1996	540 contact eczema			
Kerscher 1992	24			
Lauber 1987			34 risk (bronchial hyper-reagibility, obstructive lung disease	
Maiche 1991	25 f			
Marti 1977	50 anal fissures, hip bath			
Nasemann 1975a	38			
Nasemann 1975b	51			27
Patzelt 2000	72			
Peters 1987	50 neurodermitis			
Remme and de Witt 1984	54 ulcera crurum			
Rudzki and Jablonska 2000	982 type IV sensitizations			

Sauer 1990			53 sinusitis maxillaris	
Schmidt 1975			10 chronic obstructive bronchitis	
Stiegelmeyer 1978		104 unspecific stomach complaints		
Troll 1990			47	
total	**2,255**	**104 + 28 US**	**144**	**206**
Children				
Jeschke 2009	**817**; No information about age group/method of administration; inhalation covered; **not added below**			
6 months – 5.5years De la Motte *et al*. 1997		79 combination		
Children 1 month – 6 years Becker 2006		121 combination		
Infants Aertgeerts 1984	24 monopreparation			
Infants Weizman *et al*. 1993		34 combination		
Infants 21 days – 60 days Savino 2005		41 combination		
Infants, toddlers Viegas *et al*. 1996	55 monopreparation			
Infants, toddlers Stechele 1991	76 monopreparation			
Total **+ n=817 no diff.**	**155**	**275 combinations**		
Pregnant women (results from questionnaires) predominantly matricaria tea				
Bishop *et al*. 2011	551 no differentiation			
Cuzzolin 2010	76 no differentiation			
Facchinetti *et al*. 2012	250 no differentiation predominantly oral			
Forster *et al*. 2006	65 no differentiation			
Holst 2011		76		
Moussally *et al*. 2009		122		
Moussally 2012		20 preterm birth, part of the data above		
Nordeng 2004		13		
Sum:1,077 pregnant women used predominantly matricaria tea				

In summary 2,327 adults and 155 children have been exposed to cutaneous use of *Matricaria recutita* containing products. For the internal use there are 104 + 28 US adults published. The children

published were treated with combination products containing matricaria recutita among other herbal preparations. They are included here. The publication of Jeschke (2009) covers 817 children treated with mono-preparations but without any differentiation of the method of administration and age groups. The data regarding pregnant women are published from questionnaires.

4.6. Adverse events and serious adverse events and deaths

Hypersensitivity reactions including severe allergic reaction (dyspnoea, Quincke's disease, vascular collapse, anaphylactic shock) following mucosal contact with liquid chamomile preparations have been reported (see also 4.4).

4.7. Case reports

Subiza *et al*. (1989) reported about an 8 year-old boy having suffered from hay fever and asthma caused by a variety of pollen for the past three years. He was under immunotherapy for 2 years. One month after he stopped immunotherapy he had a night episode of coughing, slight dyspnea and wheezing. His mother tried to relieve the symptoms with a cup of matricaria tea. Several minutes later the patient deteriorated with dyspnea, loss of consciousness and shock. After medical intervention he could be stabilized. As cause an IgE mediated immunologic reaction potentially cross reacting with the known mugwort allergy could be identified (Subiza *et al*. 1989).

Scala (2006) reported on a 20-year-old woman with a proven allergy to Matricaria suffered from short-lasting rhinitis when using a matricaria-scented toilet paper. The prick-by-prick test performed with the toilet paper was positive. Diagnosis was confirmed by a challenge test that also resulted positive. Dechallenge resulted in removal of symptoms.

A 50 years-old metalworker developed acute eczema on forearms and hands, which he tried to clear with compresses and washings with tea from matricaria, Roman chamomile and mallow herbs. He was positive tested with Roman matricaria extract 1%pet in D2 and D4 and with German Matricaria tea D4 and with the combination in both dilutions (Pereira *et al*. 1997).

A 23 year-old women came with recurrent facial eczema and eczema of the back of her foot. She reacted to colophonium and potassium dichromate in the Patch test. A year later she reacted on cobalt and oak moss. Even avoidance did not solve the problem. At 25 she had further recurrences of her facial eczema. Further Testing showed reaction to matricaria, sesquiterpenlactones were negative. Roman matricaria was not tested. At last she remembered that the facial eczema eruptions followed the administration of steaming matricaria tea (Rycroft 2003).

Jensen-Jarolim *et al.* (1998) reported an anaphylactic shock due to a matricaria containing enema during labour, resulting in an asphyxia of the newborn. The enema contained a matricaria containing preparation and glycerol. After initial nausea, she developed urticarial, larynx edema, tachycardia, hypotension with loss of cardiac sounds in carciotocography. After emergency treatment (corticoids, antihistamines, volume substitution, etilefrin i.v.) she received an emergency caesarean section. The newborn had a severe asphyxia (Apgar score=0) and died the following day. IgE mediated anaphylaxis triggered during the enema was the reason.

Thien (2001) filed a case report of a 69 year-old Ukrainian, who suffered from an anaphylactic reaction following a matricaria tea enema made to treat a 3 day constipation. Within 5 minutes after the enema he developed flushing and an urticarial rash on the inside of his arms associated with dyspnoea. After an antiallergic treatment the symptoms removed. The medical history revealed a seasonal rhinitis. Skinprick tests to aeroallergens showed a reaction to ragweed (13 mm) and cypress (5 mm) and to matricaria tea as well (5 mm).

Benner and Lee (1973) published an anaphylactic reaction after oral ingestion of matricaria tea of an 35 year-old atopic female teacher, who had a known ragweed hay fever. She developed after several sips of tea abdominal cramos, thickness of her tongue and a tight sensation in her throat. Then angioedema of her lips and eyes developed, diffuse pruritus and a full sensation in her ears. After an antiallergic treatment with diphenhydramine and cortison the symptoms removed.

4.8. Laboratory findings

Laboratory data were not published.

4.9. Safety in special populations and situations

Pregnancy and Lactation

Nordeng and Havnen (2004) reported on the usage of herbal drugs during pregnancy in 400 Norwegian women. 36% (n=144) had used herbal medicinal products during pregnancy. Matricaria was amongst the 10 most commonly used herbal drugs, overall applied by 9% (n=13) of the herbal drugs using women.

In England a questionnaire concerning the use of herbal products was given to 1,037 women, at least 20 weeks pregnant, of which 578 were answered. 334 (57.8%) used at least one herbal product, 76 used matricaria. For Matricaria tea, not exceeding the use as a nutrient, there is no documented risk (Holst *et al*. 2010).

Cuzzolin *et al*. (2010) interviewed 392 Italian women regarding their use of herbal products during pregnancy. 48 women used matricaria preparations orally and topically against anxiety, digestive problems, and stretch marks. There were no statistically significant effects for matricaria user. Pregnancy outcome showed no matricaria specific issues. The reported tendency of smaller birth weight for all herbal users could not be addressed towards the herbs used.

Facchinetti *et al*. (2012) interviewed 700 women around labour in 2 university hospitals and one general hospital. 35.7% took matricaria predominantly in oral administration. A correlation (matricaria use and low body weight of the infant) assumed to be relevant, did not show to be statistically significant.

Bishop *et al*. (2011) reported about the results of an observational population-based cohort study of 14,541 pregnant women residing within the former county of Avon. Data were available from 14,115 women. 3,774 women had used CAM during pregnancy. Matricaria was used by 551 women throughout pregnancy (14.6%).

In Canada a questionnaire was submitted to 8,505 women who gave birth to a live born between January 1998 and December 2003 in one of the Quebec´s hospitals. The questionnaire was answered by 3,354 women and 9% if they used herbal products (HP) during pregnancy. Matricaria, green tea, peppermint and flax were the most frequently HP used. Matricaria tea was used by 122 women out of 356 pregnant women (Moussally *et al*. 2009). From the same data set the researchers performed a case control study regarding premature delivery (<37th week), 623 preterm childbirths were identified. 62 women used HP during pregnancy, one third matricaria. After adjusting to cofounders no relation between the use of matricaria during the last two trimesters of pregnancy and preterm delivery was found.

A questionnaire was answered by 588 Australian pregnant women (36-38th pregnancy week), from whom 11% used matricaria tea during pregnancy (Forster *et al*. 2006). Information on pregnancy outcome was not part of the questionnaire.

Assessors comment

The abovementioned studies with large numbers of pregnant women showed no risk for the use of at least matricaria teas during pregnancy. The specific information on the other preparations of the Matricariae flos monograph is too scarce to recommend a use. The case report covers a severe anaphylactic reaction, which is not a pregnancy related risk but could happen to any atopic patient reacting to asteraceae. For Matricaria tea the use in pregnancy and lactation is sufficiently documented to recommend a traditional use, since it is widely used as a herbal tea.

Since data regarding the cutaneous use of matricaria containing preparations during lactation are not available, sore nipples are nevertheless a common problem. Therefore the following text should be included under pregnancy and lactation:

"Before nursing the baby the nipples should be cleaned from matricaria containing products to prevent a sensitization of the baby."

Children

General

Jeschke *et al. (*2009) reported about the risks of asteraceae containing extracts in german primary care. 362 physicians were contacted to participate in an online system to document all prescriptions of asteraceae containing extracts with the corresponding adverse drug reactions (ADR). 107 physicians agreed to participate. 38 fulfilled the technical requirements. 55% were general practicioners, 45% specialists (23% pediatricians, 11% internal medicine, 11% others). From September 2004 - September 2006 50,115 patients were documented. Who received 199,9387 precriptions for 360,488 drugs. 18,830 Patients received 25,652 prescriptions with 42,378 remedies containing Asteraceae. ADRs were evaluated according to WHO Adverse reaction terminology. The statistical analysis showed that in children the asteraceae containing drugs were prescribed regularly (60%). The most frequently prescribed Asteracea was *Matricaria recutita* (49.9% of adult male, 32.3% of female adult, 51.7% in children). *Matricaria recutita* was predominantly prescriben as herbal monopreparation (75%). It was used for diseases of the middle ear (10.3%), oral cavity and jaws (8.3%), salivary glands, infectious diseases especially for the upper respiratory tract (16.2%). ADR´s related to Matricaria recutita were rare. The entire sample of 18,830 patients who received Asteraceae containing remedies no serious ADR was reported. In the focus group of 6,961 patients in whom non serious ADR´s were reported, 11 non serious ADR occurred.1 case was a mild allergic reaction of the skin after oral administration of a combination product containing *Artemisia abrotanum* and *Matricaria recutita* to a female 71 year-old with an acute gastroenteritis. The second case was a gastralgia during a acute gastroenteritis of a 47 year-old male adult, which was classified as possible, but could as well be connected to the underlying disease. The incidence was 2/1,602 patients (0.12%). Children were not involved.

Internal Use

Safety data could only be deduced from clinical studies with combination products.

Only two clinical trials have evaluated the efficacy of matricaria for the treatment of colic in children, and both combined matricaria with other herbs. In a prospective, randomized, double-blind, placebo-controlled study, 68 healthy term infants who had colic (2 to 8 weeks old) received either herbal tea (matricaria, vervain, licorice, fennel, balmmint) or placebo tea (glucose, flavoring). Each infant was offered treatment with every bout of colic, up to 150 ml/dose, no more than three times a day. After 7 days of treatment, parents reported that the tea eliminated the colic in 57% of the infants, whereas placebo was helpful in only 26% (P_0.01). No adverse effects were noted in either group (Weizman *et al*. 1993).

A randomized, double-blind, placebo-controlled trial of 93 breastfed term born colicky infants (21 days to 60 days) compared a standardized extract of chamomile (*M. recutita*), fennel (*Foeniculum vulgare*), and lemon balm (*Melissa officinalis*) with placebo twice a day for 1 week. Drop outs were 5 children who were not presented for the second visit and 3 children due to fever. Crying time was reduced in 85.4% of the verum group and in 48.9% of the placebo group (P_0.005). No adverse effects were reported (Savino *et al*. 2005).

In a prospective,double-blind, randomized, controlled multicenter study, 79 children from the ages of 6 months to 5.5 years who had acute, noncomplicated diarrhea were given either a liquid preparation containing apple pectin and matricaria fluid extract standardized to 2.5 g chamazulene/100 g or placebo for 3 days. Both groups received standard medical treatment of hydration and electrolyte repletion. The matricaria and apple pectin combination decreased the diarrhea more frequently than did the placebo (P_0.05) (De La Motte *et al*. 1997).

A combination product (apple pectine and matricaria extract) was investigated in a double-blind, randomised trial in children from 6 months to 6 years of age with unsprecific diarrhea (Becker et al. 2006). No serious side effects were observed that could be attributed to the verum population of 121 patients. The study is not suitable to give any information on efficacy of herbal preparation from matricaria. However, it is supportive to demonstrate the safe use in even young children.

A follow-up multicenter, randomized, double-blind, placebo-controlled parallel study of 255 children who had acute diarrhea demonstrated that the matricaria and apple pectin combination was superior to placebo in significantly reducing stool frequency. Treatment was well tolerated, with the incidence of adverse effects similar to that of placebo (Becker *et al.* 2006).

Cutaneous Use:

In an uncontrolled study 24 infants with diaper rash (11 weeks - 13 months, average age 7.5 months) were treated with extract m) as a washing and thereafter extract o) ointment. Two irritations of the skin were observed (Aertgeerts *et al.* 1984).

55 toddlers (31 w, 24 m, age range 2 weeks – 36 months) with diaper rash were treated at every diaper change with extract o) cream. In 2 children a desquamation if the skin, in two children a reddening of the skin was noted (Viegas 1996).

76 infants and toddlers, (2/3 in the age from 1-10 months), 49 with diaper rash, 9 with seborrhoic eczema, 14 with perioral eczema were treated with extract o) ointment three times a day for 8 days. No adverse events were observed (Stechele 1991).

***Assessors comment*:**
Since data regarding the cutaneous use of matricaria containing preparations during lactation are not available, sore nipples are nevertheless a common problem. Therefore the following text should be included under pregnancy and lactation:

“Before nursing the baby the nipples should be cleaned from matricaria containing products to prevent a sensitization of the baby.”

Due to the long term use and the lack of safety concerns the publication of KOOP Phytopharmaka (Dorsch 1993) could support to accept the posology published there for herbal tea in children and adolescents from 4 weeks to 18 years. However, due to general considerations of nutrition and fluid intake of children until an age of 6 months, the monograph displays the use of herbal tea of matricaria starting with the age of 6 months.

Drug Interactions:

Case reports:

Segal and Pilote (2006) reported on a 70 year-old woman, whose medical history included a mitral valve replacement and a previous episode of atrial fibrillation. She was admitted to the hospital with a cough expectoration of yellow sputum. Her medication included warfarin (4 mg 3 d/weekk; 6 mg 4 d/weekk) amiodarone, digoxin, synthroid, alendronate metoprolol and a calcium-vit. D supplement. An infection of the upper respiratory tract was diagnosed and she was discharged without further medication. 5 days later she was suffering from the same symptoms as well as dyspnoe on exertion, bipedial edema, and ecchymoses at her lower abdomen. An abdominal CT revealed a retroperitoneal hematoma of substantial amount in the pelvis as well as on the musculus rectus bilateral. After transfusion of 3 units of packed red blood cells and 2 units of fresh frozen plasma she was stabilized and discharged. On further questioning she admitted to use 2 teaspoons full of a matricaria based skin lotion to treat her pedal edema on each foot as well as up to 10 cups of matricaria tea (made from 1 teaspoon of dried matricaria leaves) to treat her sore throat. Despite an interaction between amiodarone and warfarin, both being metabolized via CYP2C9, is known, the patient had taken both substances for years without problems. Since matricaria is predominantly inhibiting CYP1A2, a pharmacokinetic interaction was ruled out by the authors. They favoured a pharmacodynamic interaction of warfarin with the coumarines contained in matricaria. This is not probable, since coumarines are contained in many herbal substances, most of them are pharmacologically inert. An interaction like this one must be quite often otherwise. The case report is not to be adducted, since a plant part was used here, which is not relevant for the monograph.

Nowack and Nowack (2005) reported on three cases of patients with cadaveric renal allografts under stable immunosuppression with cyclosporine (metabolized via CYP3A4) and mycophenolate mofetil (MMF)(metabolized via glucuronisation) changing under fluid excess via herbal teas. Two of the case reports were associated with matricaria tea.

Case A: A 48 year-old woman having cyclosporine trough levels of 110-140 µg/l under 2 x 110 mg/d developed gradually declining trough levels down to 80 µg/l under increasing doses of cyclosporine (2 x 170mg/d). Comedication was: pravastatin, valsartan, hydrochlorothiazide. The patient reported drinking up to 2 l herbal tea, as recommended by the transplantation unit. Thüringer 9 Kräuter Tee contained: *Mentha piperita*, *Rubus fruticosus*, *Matricaria recutita*, *Melissa officinalis*, *Coriandrum sativum*, *Santalum album*, *Citrus auranticum*, *Krameria triandra* and *Pimpinella anisum*. (no information on the amounts). After 2 weeks of replaced mineral waterthe trough levels of Cyclosporine increased, despite reduced doses (2 x 150 mg/d). A reexposition to the former tea led to decreasing trough levels within 2 weeks.

Case B: A 37 year-old Armenian with a cadaveric renal allograft under maintenance immunosuppression with cyclosporine and Azathioprin, later replaced with Mycophenolate Mofetil (MMF) (cyclosporine trough levels of 180 - 200 µg/l under 2 x 75 mg/die cyclosporine reported drinking at least 1.5 l of matricaria tea/day. A few weeks after having changed to rose hip tea cyclosporine trough levels declined to 100 - 120 µg/l. These levels finally dropped to 50 µg/l and the doses of cyclosporine had to be adapted (2 x 100 mg/d).

Assessors comment:

The case reports are inconsistent. Segal and Pilote argue the coumarine content as relevant for the interaction, which is not relevant for the monograph since the wrong plant parts (leaves) were used to prepare the tea. Nowack and Nowack describe contradictive effects. Case A seems to cover an interaction via CYP3A4, which is induced by a tea containing 9 herbal substances, but does not correspond to the preclinical study from Ganzera *et al*. (2006) covering the essential oil. Case B might be due to a cancelled inhibition of CYP3A4, which does not correspond to the preclinical data as well as

collected for the essential oil by Ganzera *et al*. Budzinski *et al*. (2000) demonstrated an inhibition of CYP3A4 through ethanolic standardized Canadian extracts (no specification available). Therefore the following text should be added under interactions:

"For patients after renal transplantation taking high dosages for longer periods (about two months) interactions based on effects on CYP450 have been reported."

4.10. Overall conclusions on clinical safety

The clinical safety of *Matricaria recutita* containing preparations is good. The main risk is a sensitization in cutaneous use, which is minor. For children there are data from 817 patients with an allerginicity of 0.12% (Jeschke *et al.* 2009). 3,851 adults having an indication for allergy testing showed a risk of Asteraceae allergy of about 3.1% in adults. 56% thereof were allergic to matricaria (Hausen 1996). This risk is covered by a contraindication.

To prevent sensitization of breastfed babies a note has to be introduced into the monograph under lactation:

"Before nursing the baby the nipples should be cleaned from matricaria containing products if applicable to prevent a sensitization of the baby."

Other specific risks for children of any age group are not deducible. Pregnant women may use herbal tea, for all other preparations there is a lack of data.

The drug interaction data are inconclusive from preclinical assessment to case reports. Nevertheless interactions regarding Cyclosporine immunosuppression after renal transplants are possible. Therefore a note should be entered in the monograph:

"For patients after renal transplantation taking high dosages for longer periods (about two months) interactions based on effects on CYP450 have been reported."

5. Overall conclusions

The medicinal use of preparations containing Matricariae flos has been documented for millennia in Europe and all over the world. The multitude of preparations from the different countries of Europe attest to that.

Only one clinical study of good quality has been identified (Amsterdam *et al.* 2009*)*. As the studied indication (generalized anxiety disorder) is not authorised in a medicinal product in the EU since at least 10 years a well-established use cannot be accepted for the monograph.

Accumulating the vast data from preclinical sources and from the traditional literature as well as from different clinical studies of mostly mediocre quality and from registered or authorised medicinal products in the EU the traditional use of Matricaria flos can be accepted for the following indications for adolescents, adults and elderly. The acceptable use in children is indicated (relevant age in brackets) for those herbal preparations, where safety is sufficiently demonstrated.

Indication 1: Traditional herbal medicinal product used for the symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms

Herbal preparation: a) (children 6 months – 12 years), b), d) e) (children 6 – 12 years), g) (children 6 – 12 years), h) (children 6 – 12 years), i), j), k), l) (children 6 – 12 years), m) (children 6-12 years), in the specified posologies

Indication 2: Traditional herbal medicinal product used for the relief of symptoms of common cold

Herbal preparation a), d) (children 6-12 years), e), g), h) (children 6 – 12 years), k), l), m) in the specified posologies

Indication 3: Traditional herbal medicinal product for the treatment of minor ulcers and inflammations of the mouth and throat.

Herbal preparation: a), c), d), e), h) (children 6 – 12 years), i), j), k), l), m), in the specified posologies

Indication 4: Traditional herbal medicinal product used for adjuvant therapy of irritations of skin and mucosae in the anal and genital region, after serious conditions have been excluded by a medical doctor.

Herbal preparation:a), c) d), e), f) (children 6-12 years), g), h), i), j), k), l), m)(children 6-12 years), o), p)

Indication 5: Traditional herbal medicinal product used for the treatment of minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).

Herbal preparation: a), c), d), e), f) (children 6-12years), g), i), k), l), m), n) (children 4 weeks (wounds only) - 12 years.) o), p) (children 6 months – 12 years) in the specified posologies.

No sufficient clinical evidence could be identified for Matricariae aetheroleum except the observational data from Marti 1977. Based on pharmacological data and medicinal products authorised or registered in the EU the traditional use is acceptable for adolescents, adults and elderly in the indication:

Traditional herbal medicinal product used for adjuvant therapy of irritations of skin and mucosae in the anal and genital region, after serious conditions have been excluded by a medical doctor.

Regarding safety, notes are added under lactation concerning the cleansing of the nipples before nursing, and under interactions precautions due to possible interactions for patients under immunosuppression from cyclosporine after renal transplants.

Safety

The main safety issues are senzitation regarding allergies towards asteracea. Jeschke *et al.* (2009) published data from 1,602 patient where the reported allergies were 0.12%. The labeling has to be adapted.

The preclinical data refer to an inhibition of CYP450 3A4, reflected by a clinical case report, where the interaction occurred after an intake of 2-3 l Matricaria containing tea, which is to be labeled under interactions.

The use in pregnant women is to be excluded according to the lacking posologies. Only tea can be recommended in pregnant women, for the other preparations there are no specific data.

Risk Benefit assessment:

Since no further risks than allergenicity and sensitization are noteworthy the benefit risk relation for the traditional use is to be assessed as positive.

A community list entry is not possible, due to lacking data on genotoxicity.

Annex

List of references