EUROPEAN MEDICINES AGENCY
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Committee on Herbal Medicinal Products (HMPC)

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

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Matricaria recutita* L., flos *Matricaria recutita* L., aetheroleum
Herbal preparation(s)	a) Comminuted herbal substance a1) Essential oil b) Liquid extract (DER 1:1), extraction solvent: ethanol 96% V/V: water: ammonia solution 10% m/m (50:47.5:2.5) c) Liquid Extract (DER 1:4.3-5.7), extraction solvent: ethanol 96% V/V: water: ammonia solution 10% m/m (50:47.5:2.5) d) Liquid extract (DER 1:1), extraction solvent: ethanol 48% V/V: ammonia solution 10% m/m (39:1) e) Liquid extract (DER 1:1), extraction solvent: ethanol 45% V/V: ammonia solution 10% m/m (14.7:1) f) Dry extract (DER 4-7:1), extraction solvent: ethanol 50% m/m g) Liquid Extract (DER 1:1.7-2.6), extraction solvent: ethanol 48% V/V h) Liquid extract (DER 1:1), extraction solvent: ethanol 55% V/V i) Liquid extract (DER 1:2), extraction solvent: ethanol 70% V/V j) Liquid extract (DER 1:4.1-4.6), extraction solvent: ethanol 55% V/V: Poloxamer 188 (993:3) k) Liquid Extract (DER 1:1.8-2.1), extraction solvent: ethanol 52% V/V: macrogol hydroxystearate (99.5:0.5)

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	l) Liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) m) Liquid extract (DER 2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide). n) Dry extract (DER 11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) o) Liquid extract (DER 1:2.0-2.8), extraction solvent: propan-2-ol 48% V/V
Pharmaceutical form(s)	Herbal substance or comminuted herbal substance as herbal tea for oral use and inhalation. Herbal preparations in liquid dosage forms for oral use. Herbal substance or comminuted herbal substance for infusion preparation for oromucosal use or cutaneous use. Herbal preparations in liquid dosage forms for preparation of dilutions for oromucosal 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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Table of contents

1. Introduction

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

- Herbal substance(s), Herbal preparation(s)

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

- European Pharmacopeia (Ph. Eur. 8.0)
- German Kommission E monographs (1984)
- British Pharmacopeia (2008)
- British Herbal Pharmacopeia (1983)
- ESCOP Monographs (2003)
- WHO Monographs (1999)
- United States Pharmacopeia 29 / NF24 (2006)

The botany of matricaria and the phytochemical characterisation of the essential oil was reviewed (Carle and Gomaa 1992a; Blaschek *et al.* 2011). The herbal substance consists 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 (Ph. Eur. 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 aetheroleum, monograph (Ph. Eur. 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 (Ph. Eur. 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 apigenin-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
- spiroethers (cis- and trans en-in-dicycloethers)
- phenolic acid
- 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-in-dicycloethers)

(Blaschek *et al.* 2011; Wichtl and Bauer 2009; Barnes *et al.* 2007; ESCOP 2003; Sticher *et al.* 2015; Mann and Staba 1986; Mulinacci *et al.* 2000*;* Barene *et al.* 2003*;* Matos *et al.* 1993; Mimica-Dukic *et al.* 1993*;* Stanev *et al.* 1996, Pino *et al.* 2002*;* Pino *et al.* 2003)

Herbal teas prepared from matricaria flowers are mainly containing flavonoids and their glycosides, mucilaginous constituents and only minor amounts of constituents of essential oil (about 10 to 15% depending on conditions of herbal tea preparations). The coumarines herniarin and umbelliferone are also soluble in hot water, especially matricin is extracted in concentrations which are pharmaceutically relevant (Schilcher 1987; Mulinacci *et al.* 2000).

Cultivars and different proveniences of matricaria flowers vary substantially with respect to the composition of constituents. 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 is 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, they are specified separately.

1.2. 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, 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. Data on medicinal use

2.1. Information about products on the market

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

Matricaria recutita L. is one of the most popular medicinal plants in Europe. Accordingly a number of herbal medicinal products with herbal preparations of matricaria flowers have been authorised in Member States of the EU. There was also a herbal medicinal product with Matricaria oil as active substance, which is suitable to demonstrate a tradition of medicinal use for more than 30 years. The following table is giving an overview.

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Matricariae flos	Mild gastrointestinal disorders, irritation of the oropharyngeal mucosa and of the upper respiratory tract	Tea bags containing 1.0 g or 1.5 g Herbal tea: 1.5 g 3-4 times daily Herbal tea:1.0 g several times daily; throat washing 3 min; inhalation 5-10 min	Austria, TU
Liquid extract (DER 1:4 – 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 l)		As oral liquid and semi-solid dosage form in a strength of about 14.88% in base	Since 2002 Austria, WEU
Extract EtOH 38.5% (m/m) (DER 1:4-4.5), containing 50 mg bisabolol and more than 150 mg apigenin-7-glucoside (corresponds to liquid extract l)	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 per day; no administration to children <12 years Cutaneous use/bath additive: irrigation, wound dressings and partial baths: 15 ml/l; full bath: 2 times 15 ml (or more, depending on need) Duration of use: 10 min Use as mouthwash: 2-3 ml to maximum 5 ml in half a cup of lukewarm water; gargle for 1-2 min Pure (no dilution): Oromucosal use: dab acute infections in mouth	Since 1995 Belgium
Extract EtOH 95.4% (V/V) (DER 2.75:1) containing minimum 20 mg essential oil, minimum 7 mg levomenol (corresponds to liquid extract m)	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.	Since 2005 Belgium

Active substance	Indication	Pharmaceutical form	Regulatory Status
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.	Herbal tea: Oral use: 1.5 g/250 ml; 3 times 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	Czech Republic
Matricariae extractum corresponding to Ph. Eur.; 33 g/100 g of the solution (corresponds to liquid extract b)	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 times 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 times daily	Since 1969 Czech Republic
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	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 times daily	Since 1999 Czech Republic
Matricariae extractum siccum 4.8-6.3:1, ethanol 95.4% (V/V); 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	10 mg/1 g of the ointment For cutaneous use: several times daily	(not included as originating from 1999; there is no tradition of medical use for 30

Active substance	Indication	Pharmaceutical form	Regulatory Status
	genital area, lips inflammations and inflammations of nipples during breastfeeding; for treatment of dry eczema.		years), Czech Republic
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.	1 ml (= 20 drops) contains 1 ml liquid extract Cutaneous use in children from 6 years of age, adolescents and adults: Skin inflammations: several times daily compresses and irrigations 1 ml /100 ml water or several times daily partial baths 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 children from 6 years of age, adolescents and adults: 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 children from 12 years of age, adolescents and adults: 3 to 4 times daily 60 drops (3 ml)/150 ml water	Since 1976 Germany
Dry extract (4-7:1), extraction solvent: ethanol 50% m/m (corresponds to dry extract f)	Skin inflammations after ultraviolet irradiation (sun burn).	100 g (= corresponding to 98.1 ml) liquid contains 0.4668 g dry extract Children from 6 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.	Since 1976 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
Liquid extract (1:4-4.5), 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 l)	For compresses, irrigation or baths 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 children from 6 years of age, adolescents and adults: For impregnated dressings and irrigations: 45 ml per 1 l water, 1 to 2 times daily. For partial and hip baths: 30 ml per 1 l water, 1 to 2 times daily	Since 1976 Germany
Liquid 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 m)	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.	Since 1983 Germany
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.	100 ml solution contain 95.8 g extract 1 ml corresponds to 20 drops Children from 6 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 Adolescents and adults: 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 baths 15 ml per 1 l hot water several times daily	Since 1976 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
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.	For internal use: children between 6 and 12 years of age: up to 4 times daily 2.5 ml/150 ml water Adolescents and adults: 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 baths: 10 ml per 1 l water several times daily For mouth rinsing or gargling: 2.5 ml in 125 ml water 3 to 4 times daily For inhalation: 5 ml/150 ml water	Since 1976 Germany
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.	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 baths:15-30 ml in 5 l warm water, one to several times daily	Since 1976 Germany
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 irrigation or rinsing of	100 ml liquid (=93.45 g) contains: 93.45 g extract For impregnated dressings and irrigations:	Since 1976 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
(corresponds to liquid extract j)	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.	40 ml per 1 l water, one to several times daily For partial and hip baths: 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) (corresponds to liquid extract c)	Inflammations of the skin and of the oropharyngeal mucosa.	100 ml liquid contains 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 an impregnated dressing with the infusion. 10 ml with 150 ml hot water	Since 1976 Germany
Liquid extract (1:1.8-2.1), extraction solvent: ethanol 52% V/V: macrogol hydroxystearate (99.5:0.5) (corresponds to liquid extract k)	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 baths 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	Since 1990 GDR product 1983

Active substance	Indication	Pharmaceutical form	Regulatory Status
		baths: 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 (1:2-2.8), extraction solvent: propan-2-ol 48% V/V (corresponds to liquid extract o)	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 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.	100 ml solution contains 94.2 g extract 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	Since 1976 Germany
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.	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	Since 1976 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
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 n)	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.	Since 1976 Germany
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 baths and irrigations.	Oral use: 3 g/150 ml water; 3-4 times 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	Since 1982 Germany
Liquid extract (1:4-4.5), extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide)	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 and 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 and elderly: Single dose: 20 ml per 1 l hot water Daily dose: 1-2 times daily Gargling rinsing mouth and throat:	Since 1978 Germany

Active substance	Indication	Pharmaceutical form	Regulatory Status
		Adolescents, adults and elderly: Single dose: 5 ml per 100 ml warm water Daily dose: 3 to several times For washings, impregnated dressings and irrigations: Adolescents, adults and elderly: 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	
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 baths and irrigation of irritations of skin and mucosae in the anal and genital region. 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 Duration of use: 10-20 minutes	Since 1976 Germany
Dry chamomillae flower extract, (15-25:1), extraction solvent: ethanol 95.4% V/V	Adjuvant treatment of small inflamed wounds: - inflammation of the skin, e.g., mild sunburn, or following X-ray or UV irradiation	Ointment 4.3 mg/g Cutaneous use: Apply several times per day	Since 2004 Latvia

Active substance	Indication	Pharmaceutical form	Regulatory Status
	- 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		
Chamomillae anthodium Herbal substance Poland 1-10)	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	Herbal tea: 2.4-4 g / 2-4 times 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)	Before 1980 Poland

Active substance	Indication	Pharmaceutical form	Regulatory Status
	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.		
Chamomillae anthodii extractum (1:5, ethanol)	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 times daily Cutaneously for washings and compresses: 5 ml/100 ml (or 10%) Mouth washings: infusion 3%	(not included into the monograph, period of tradition is > 15 years, but shorter than 30 years, exact solvent concentration is missing) Poland
Chamomillae anthodii extractum (1:1; ethanol-water)	First degree burns (also solar), bedsores, minor abrasions.	Ointment: Smear skin 1-3 times daily	(not included into the monograph, period of tradition is > 15 years, but shorter than 30 years, exact solvent concentration is missing) Poland
Chamomillae anthodii extractum fluidum (1:2, 70% V/V) ethanol) (corresponds to liquid extract i), extraction solvent 70% V/V)	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. Traditionally cutaneously in skin and oral cavity (oromucosal, throat, gingival) inflammations. Orally as auxiliary spasmolytic, carminative and anti-	Orally: 3-4 times daily 5 ml in water. Cutaneously in 10% solution in boiled water. Orally 2.5-5 ml /50-100 ml 3 times daily Cutaneously for washings and impregnated dressings, 5 ml/100 ml (or 10%) Mouth washings: infusion 3%	before 1980 Poland

Active substance	Indication	Pharmaceutical form	Regulatory Status
	inflammatory in gastrointestinal inflammations.		
Chamomillae unguentum	Traditionally in skin inflammations.	Smear skin 1-3 times daily	(not included into the monograph, period of tradition is > 15 years, but shorter than 30 years, details are not available), Poland

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

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

Since ancient times traditional use of herbal preparations from matricaria have been reported. Benedum *et al.* (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) and 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.

Monographs related to efficacy and safety

The Kommission 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 2003

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Matricariae flos	External: Inflammations of the skin and mucosa as well as bacterial skin diseases including buccal cavity and gingiva. Inflammations and irritations of the respiratory tract (inhalation). Diseases of the anal and genital area (bath and irrigation). Internal: gastrointestinal spasms and inflammations	Infusion with nearly 3 g chamomile flos and nearly 150 ml hot water, cover for 5 to 10 min and then filter with a tea strainer. If not differently advised by a doctor, drink one cup of freshly prepared tea 3 to 4 times daily between meals in case of gastrointestinal disorders. In case of inflammations of the oropharyngeal mucosa gargle several times daily with freshly prepared tea. External use: Infusion of 3 to 10% for compressions and irrigations, as bath additive 50 g herbal substance per 10 l water, semisolid preparations with preparations equivalent to 3 to 10% herbal substance.	Commission E, Banz Nr.: 228 from 05.12.1984

2.3. Overall conclusions on medicinal use

Based on products existing in the market for more than 30 years, corresponding monographs on Matricariae flos and diverse contributions in the scientific literature traditional use is demonstrated for a broad set of herbal preparations of *Matricaria recutita*, flos and also the Matricaria oil (see table 2.3). The data described in section 2.1 and 2.2 reveal five different indications which were acceptable for a traditional use monograph. The wording in the respective two monographs was adjusted to the wording used for similar indications. For 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", which is included in both monographs, the exclusion of serious conditions by a medical doctor was regarded necessary to ensure adequate usage.

Table 3: Overview of evidence on period of medicinal use of *Matricaria recutita*, flos and herbal preparation derived thereof and *Matricaria recutita*, aetheroleum in the order of the monograph. Matricaria oil is integrated as a1).

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

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance a) Herbal tea; oral use, oromucosal use	Symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms.	Oral use: Adolescents, adults and 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: 1.0-1.5 g DD: 2-4 times Children 6 months-2 years: SD: 0.5-1.0 g DD: 2-4 times	PL before 1980 Dorsch *et al.* 1993

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Relief of symptoms of common cold:	Inhalation: Adolescents, adults and elderly: 3-10 g/100 ml water DD: several 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 and elderly: SD: 1-5 g in 100 ml water DD: several times	PL before 1980
	Irritations of skin and mucosae in the anal and genital region.	Irrigation: Adolescents, adults and elderly: SD: 4.5-5 g/l water DD: several times	PL before 1980
	Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Adolescents, adults and elderly: SD: 3-10 g/100 ml water DD: several times	PL before 1980
a1) Essential oil	Irritations of skin and mucosae in the anal and genital region	Adolescents, adults and elderly: SD: 0.5 to 1 mg per l for partial baths or full baths DD: 1 or 2 partial baths per day One full bath per day or every other day Duration of use: 10-20 minutes	DE 1976
b) Liquid extract (DER 1:1), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% m/m (50:47.5:2.5) Liquid for oral use	Symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms	Adolescents, adults and elderly: SD: 2 g/150 ml water DD: 3-4 times	DE 1976

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
c) Liquid Extract (DER 1:4.3-5.7), extraction solvent: ethanol 96% V/V : water : ammonia solution 10% m/m (50:47.5:2.5)	Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and 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 and elderly: SD: 10 ml/150 ml water DD: 3-4 times	DE 1976
d) Liquid extract (DER 1:1), extraction solvent: ethanol 48% V/V : ammonia solution 10% m/m (39:1)	Symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms.	Adolescents, adults and elderly: SD: 3 ml/150 ml water DD: 3-4 times	DE 1976
Liquid for oral, inhalative, oromucosal, cutaneous use	Relief of symptoms of common cold.	Adolescents, adults and 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 and 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 and elderly: SD: 1.5 ml/150 ml water DD: several times Partial baths: SD: 5 ml per 1 l water DD: several times	DE 1976
	Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Adolescents, adults and elderly: Compresses and irrigations:SD: 1.5 ml/150 ml water DD: several times	DE 1976

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
e) Liquid extract (DER 1:1), extraction solvent: ethanol 45% V/V : ammonia solution 10% m/m (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 and 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 and elderly: SD: 5 ml/150 ml water DD: several times	DE 1976
	Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and 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 and elderly: SD: 20 ml/l water for compresses and irrigation SD: 10 ml/l water for partial baths DD: several times	DE 1976
	Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Adolescents, adults and elderly: SD: 20 ml/l water for compresses and irrigation SD: 10 ml/l water for partial baths DD: several times daily	DE 1976
f) Dry extract (DER 4-7:1), extraction solvent: ethanol 50% m/m Liquid for cutaneous us	Minor inflammation of the skin (sunburn).	(in diluted liquid dosage forms containing approximately 0.47% dry extract) Adolescents, adults and elderly: SD: few drops on affected skin DD: several times	DE 1976
g) Liquid extract (DER 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. Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and 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

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Relief of symptoms of common cold.	Adolescents, adults and elderly: SD: 15 ml/l hot water DD: 1-2 times	DE 1976
	Irritations of skin and mucosae in the anal and genital region.	Adolescents, adults and elderly: SD: 15 ml/l hot water DD: several times	DE 1976
	Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Adolescents, adults and elderly: SD: 15 ml/l hot water DD: several times	DE 1976
h) Liquid extract (DER 1:1), extraction solvent: ethanol 55% V/V Liquid for inhalative, oromucosal and cutaneous use	Relief of symptoms of common cold.	Adolescents, adults and elderly: SD: 15 ml/l water DD: 1-3 times DD: up to 4 times	DE 1976
	Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and elderly: SD: 1-2 ml/150 ml warm water DD: up to 4 times Children 6-12 years: SD: 0.5-1 ml/150 ml warm water DD: up to 4 times	DE 1976
	Irritations of skin and mucosae in the anal and genital region Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Impregnated dressings and irrigation Adolescents, adults and elderly: SD: 15 ml/l warm water DD: 1-several times Partial baths SD: 15-30 ml/5 l warm water DD: 1-several times	DE 1976
i) Liquid extract (DER 1:2), 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. Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and elderly: SD: 2.5-5 ml/50-100 ml water DD: 3-4 times	PL before 1980

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Adolescents, adults and elderly: SD: 5-10 ml in 100 ml water for washings and compresses DD: several times	PL before 1980
j) Liquid extract (DER 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 and elderly: SD: 5 ml/150 ml warm water DD: 3-4 times	DE 1976
	Relief of symptoms of common cold.	Adolescents, adults and elderly: SD: 40 ml/l water DD: 1-2 times	DE 1976
	Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and elderly: SD: 5 ml/100 ml water DD: 3 times	DE 1976
	Irritations of skin and mucosae in the anal and genital region.	Irrigation, Impregnated dressings Adolescents, adults and elderly: SD: 40 ml/l water DD: 1-several times Partial baths: 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 and elderly: SD: 40 ml/l water DD: 1-several times	DE 1976
k) Liquid extract (DER 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 and 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 1983
	Relief of symptoms of common cold	Adolescents, adults and elderly: SD:10-20 ml/l water DD: 1-several times	DE 1983

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and elderly: SD: 0.7-1 g/75 ml water DD:1-several times	DE 1983
	Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Washing dressing: Adolescents, adults and elderly: SD:10-20 ml/l water DD: 1-several times	
	Irritations of skin and mucosae in the anal and genital region.	Hip baths and irrigations: Adolescents, adults and elderly: SD:7.5-15 ml/l water DD: 1-several times	DE 1983
l) Liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) Liquid for oral, inhalative, oromucosal, cutaneous use	Symptomatic treatment of minor gastro-intestinal complaints such as bloating and minor spasms.	Adolescents, adults and 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 and elderly: SD:20 ml/l water DD:1-2 times	DE 1978
	Minor ulcers and inflammations of the mouth and throat.	Adolescents, adults and elderly: SD: 5 ml /100 ml water DD: 3 to several times	DE 1978
	Irritations of skin and mucosae in the anal and genital region. Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Impregnated dressings and irrigation Adolescents, adults and elderly: SD: 45 ml/l water DD: 1-2 times Partial bath: SD: 30 ml/l water DD: 1-2 times	DE 1976

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
m) Liquid extract (DER 2.7-5.5:1), 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. Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	For both indications: Adolescents, adults and elderly Children 6-12 years Children 2-6 years Children 4 weeks-2 years Apply a thin layer on the affected area. cream corresponds to app. 8% herbal substance DD: 2-3 times	DE 1983
n) Dry extract (DER 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. Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	For both indications: Adolescents, adults and elderly: Apply a thin layer on the affected area. in semi-solid dosage forms corresponding to app. 5.5% herbal substance DD: several times	DE 1976 DE 1976
o) Liquid extract (DER 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. Minor inflammation of the skin (sunburn) and superficial wounds and small boils (furuncles).	Partial baths: Adolescents, adults and elderly: SD: 20-40 ml/20-40 l water DD: once Full baths: Adolescents, adults and elderly: SD: 30 ml/150 l water DD: once Children 4 weeks-12 years SD: 10-20 ml/10-20 l water DD: once Irrigations, dressings: Adolescents, adults and elderly: SD: 20 ml/l water DD: 1-several times	DE 1976 DE 1976 DE 1976 DE 1976

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

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, tumour necrosis factor α (TNF-α), 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 TNF-α (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, the 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 *Matricaria 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 hours at 70°C. The extract was filtered and the filtrate was evaporated under reduced pressure and freeze dried (14 g extract). The extract at doses of 100, 300 and 1000 mg/kg was dissolved in a vehicle of 10% ethanol, 10% Tween 80 and 80% physiological saline solution and then 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 oedema 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, 0.8 mg/ml en-in-dicycloethers, 0.02 mg/ml azulenes. One ml of extract corresponded to 50 mg dry extract. Each group of 40 animals was 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 oedema 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 group, treated with 0.45 mg benzydamine, used as a positive control. However, 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 inflammation in mice subjected to croton oil induced oedema. 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 pulverised. One hundred grams plant material was extracted with 1 l ethanol 37% in a soxhlet apparatus. The extract was lyophilised. 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, malondialdehyde (MDA) and reduced glutathione (GSH) in whole blood and gastric tissue, 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). This effect, at least in part, depends upon the reduction in lipid peroxidation and augmentation in antioxidant activity.

Al-Hindawi *et al.* (1989) analysed extracts from *Matricaria recutita* flowers by means of the rat paw oedema assay. Approximately 50 g of dried plant material was extracted with 80% ethanol (3 times 500 ml; no information whether V/V or m/m) by shaking for 3 hours 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. Four hundred mg/kg extract reflecting 1.62 g fresh plant equivalent/kg inhibited rat paw oedema at 41.1% of control (p>0.01).

Essential oil

Kobayashi *et al.* (2005) determined the antipruritic effect of the ethyl acetate extract or essential oil of matricaria flowers after single oral administrations in male ddY mice (12 mice per observation). 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 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 inflammation in mice subjected to croton oil induced oedema (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 oedema. 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 hour then injected with stimulant lipopolysaccharide (LPS) (Smolinski and Pestka 2003). Apigenin inhibited LPS-induced IL-6 (65% less than control) and/or TNF-α production (76% less than control) in the serum of the mice. Apigenin showed anti-inflammatory activity in carrageenan induced rat paw oedema (Al-Hindawi *et al.* 1989; Gerritsen *et al.* 1995).

Panés *et al.* (1996) injected male Sprague-Dawley rats intraperitoneally with rTNF (rat Tumour 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 and Hirschelmann (1998) tested constituents of topical matricaria preparations in inflammations of the mouse ear induced by arachidonic acid, phorbol myristate acetate and oxazolone. Bisabololoxide A and B showed an anti-inflammatory effect comparable to bisabolol. Matricin and chamazulen (1 times 10^{-6} molar each) seemed to be a little less effective, but the slow transformation from matricin to chamazulene at the skin has to be considered. The en-in ether, predominantly the cis form, showed a good anti-inflammatory effect contrarily to *in vitro* data. Apigenin was more effective than apigenin-7-glycoside.

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 (not exactly matching the herbal preparations included in the monograph) as well as constituents thereof showed 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 6 for each model: animals in the test group were treated with the aqueous extract of *Matricaria recutita* (120 mg/kg per 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 a 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 (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 seconds. 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.

Gastrointestinal effects

In vitro

Matricaria extracts

Using 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, lyophilised, 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

Matricaria extracts

The effect of a herbal combination product (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/mouse). 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 diarrhoea (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. A certain plausibility concerning the antispasmodic effects can be retrieved from that 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 moulds and yeast, while alcoholic extracts showed higher activities against bacteria (Al-Ismail and Talal 2003).

Antimicrobial activity of the aqueous extract of *Matricaria 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% inhibition in iso-sensity-agar-assays. The antifungal activities of the German matricaria oils

against *Aspergillus niger*, *Aspergillus orchraeus* and *Fusarium culmorum* were 63-75% of inhibition of growth versus controls.

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 lyophilised 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 extract i.p. (n=15) and reached a maximum inhibition of 92.1-97.5%, compared to controls (n=15) 1.5-2.5 hours 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. The matricaria extract 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 hour, has benzodiazepine-like hypnotic activity to be antagonised 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 ovarectomised 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, behaviours 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 behaviours 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 different doses of apigenin (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). Because of the lack of effect with the addition of a benzodiazepine agonist to apigenin treated animals, the conclusion was drawn 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. The authors suggested 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. Pharmacodynamic interactions

No information available.

3.1.5. Conclusions

See 3.4

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

Absorption, Distribution, Metabolism, Elimination

There are no data available.

Pharmacokinetic interactions

In vitro

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 (details not specified) (Budzinski *et al.* 2000). Whether these data are transferable to matricaria tea has yet to be determined (see section 4.9; Nowack and Nowack 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 (characterised 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

Matricaria extracts

Maliakal and Wanwimolruk (2001) reported on the effects of herbal teas on hepatic drug metabolising enzymes in rats. Six groups of 5 female Wistar rats each had free access to peppermint, dandelion and matricaria tea (2% w/w 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 ($p \leq 0.05$) 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. However, there is only anecdotal clinical evidence for interactions for a specific group of patients after a renal transplantation.

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

3.3.1. Single dose toxicity

No data available.

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

Matricaria extracts

Kalantari *et al.* (2009) studied a matricaria containing preparation (no further details available) from Iran in a 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 hours intervals. Blood samples were prepared 48 hours 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. The authors do not provide information on mean and variance of the results. 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 showed no significant genotoxicity up to 64.7 mg/ml dry weight of extract.

Essential oil

Hernández-Ceruelos *et al.* determined in 2002 the inhibitory effect of matricaria aetheroleum (5, 50 and 500 mg/kg), on the sister chromatid exchanges (SCEs) produced by daunorubicin (10 mg/kg) or

methyl methanesulfonate (MMS: 25 mg/kg, matricaria aetheroleum 250, 500 and 1000 mg/kg) in mouse bone marrow cells. The results indicated a dose-dependent inhibitory effect on the SCEs formed by both mutagens. In the case of daunorubicin, a statistically significant result was observed in the 3 tested doses: from the lowest to the highest dose, the inhibitory values corresponded to 25.7, 63.1 and 75.5%.

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 leukaemia 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 which do not comply with current guidelines.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

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 plausibility of 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

Pharmacodynamic data exist mainly for the cutaneous use.

The antiphlogistic effect of m) liquid extract (DER 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 a cream basis and a hydrocortisone containing cream using reflexphotometry (Wells Test). Six healthy male and female probands were included. A tesafilm stripping and the identification of treatment areas at the back were used. Every hour for 8 hours 10 control points/area were checked. The evaluation was an 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. The verum cream showed a slightly better effect than placebo, 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 mins the skin of 20 healthy adults (28-42 years, male and female) was washed with water and then air dried. For 4 days the relevant ointment (extract n); base; 0.1% hydrocortisone acetate in base of extract n) containing product) were administered 2-3 times a day. 2 hours thereafter the skin profile was measured. Baseline measurement was done every 2 days 3 times on the untreated skin. The study demonstrated the antiphlogistic effect of a matricaria extract in a detergent damage of the skin (Nissen *et al.* 1988).

Kerscher (1992) irradiated the skin of 24 probands (age 23-35 years; 11 male, 14 female) on their back in 8 areas with a Waldmann UV 800 lamp with 20-160 mJ/cm^2. Thereafter either liposomal Matricariae flos dispersion extract 10% or base1 or liposomal gel preparation of matricaria flos (2%) or base2 or Matricariae flos containing cream or base3 or hydrocortisone 1% ointment or hydrocortisone 0.5% ointment were applied for 2 days. The assessment of the redness was done with a Minolta Chronometer CR200 on a Likert Scale (0=strong; 1=weak; 2=no effect). The resulting anti-inflammatory effect was strongest under hydrocortisone 1% (100%); effect for Matricariae flos containing cream was 72% and for base 50%.

Korting *et al.* (1993) showed anti-inflammatory effects of a matricaria containing cream (20 mg/g extract n) cream) compared to 1% hydrocortisone cream and to 2 different concentrations of hamamelis containing creams (oil in water emulsions containing distillate of *Hamamelis virginiana*; 0.64 mg or 2.56 mg hamamelis ketone per 100 g) in UV erythema tests (24 probands) and cellophane tape stripping tests at the back skin of 24 healthy probands compared to suitable bases measured by visual score and chronometry. The antiphlogistic effect of the matricaria containing preparation was a little less than the lower hamamelis dose and both less than 1% hydrocortisone. Twelve 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 hours (cellophane tape stripping test).

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 Generalised 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)

Oromucosal use

Nasemann and Menzel (1975) treated 29 outpatients and 49 in-patients 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 l) liquid extract (DER 1:4-4.5) 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.

Assessors comment
The study supports the antiphlogistic effects of rinsing with liquid extract l), but due to lacking controls does not support the well-established use. Traditional use is covered for oromucosal use.

Carl and Emrich (1991) tested liquid extract l) (DER 1:4-4.5) 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 tumours) and 78 patients receiving different polychemotherapies (n=46 prophylactic; 32 with established mucositis). Patients were recommended to use 10 to 15 drops in 100 ml of warm water for irrigation and rinsing at least 3 times daily. 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 1 mucositis.

Assessors comment

The study supports the hypothesis of a prophylactic efficacy of application of liquid extract l) rinsing under polychemotherapy, but cannot be regarded confirmative due to lacking controls. The study is irrelevant for the traditional use because there is no documented medicinal use in this indication for more than 30 years. An antiphlogistic effect of Matricariae flos in oromucosal use is supported.

In a double blind placebo controlled prospective clinical study with two arms, Fidler reported about the prophylactic use of liquid extract l) (DER 1:4-4.5) 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 times per day after a cooling of the mouth (icelozenges) for 30 min before polychemotherapy as an add-on. One hundred sixty-four patients receiving the first cycle of a 5-fluorouracil containing polychemotherapy sucked ice cubes for 30 min (Fidler *et al.* 1996).

Assessors comment

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 not appropriate. An antiphlogistic effect of Matricariae flos in oromucosal use is supported.

Inhalation

In an open uncontrolled study Troll and Patzelt-Wenczler (1990) reported of 47 patients with different inflammatory diseases (sinusitis, pharyngitis, tonsillitis) using either liquid extract l) (DER 1:4-4.5) 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 l) 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.

Assessors comment

No further criteria were 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 times per day with 20 ml/1 l hot water l) liquid extract (DER 1:4-4.5) 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 (4 point Likert scale) and tolerance were documented (Sauer 1990).

Assessors comment

The study documents the use as inhalation but does not support efficacy for well-established use, due to lacking controls.

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 per day 25 drops of liquid extract l) (DER 1:4-4.5) 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).

Generalised Anxiety disorder (GAD)

In a randomised, double-blind, placebo-controlled GCP conform clinical trial in parallel groups 61 patients with GAD 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 Interview for 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 *Matricaria recutita* or other Asteraceae; concomitant medication with anxiolytics, antidepressants, mood stabiliser, sedatives, or CAM remedies (e.g.: Hypericum) or other matricaria preparations was excluded. Four patients dropped out due to screen failure (3 withdrawn consent, 1 non-compliant). After randomisation 28 patients received: matricaria extract standardised 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 was achieved by a adding a disk of 1%matricaria oil or neutral oil to the lid of each airtight medication container.

Posology

1. week: 1 capsule containing 220 mg Matricaria extract per day
2. week: 2 capsules containing each 220 mg Matricaria extract per day

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

3. week: 3 capsules containing each 220 mg Matricaria extract per day
4. week: 4 capsules containing each 220 mg Matricaria extract per day

Patients continuing to have a ≥50%/baseline reduction were treated in weeks 5-8 with 5 capsules per day.

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.

Regression models were used to test the primary hypotheses. Last observation 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 a 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 and Menzel (1975) reported in his above mentioned study the use of a liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l) in 7 patients suffering from dermatitis hypostatica with contact sensitation. This supports the traditional cutaneous use.

One hundred sixty-one eczema patients were treated initially in the acute stage with diflucortolonvalerat for 3-14 days. When only an erythema with a slight infiltrate were seen, the left side was treated with a liquid extract (DER 2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= liquid extract m). The right side was treated with either 0.25% hydrocortisone, 0.75% fluocortinbutylester cream or with 5% bufexamac (cream). In the evaluation extract m) was estimated as good as 0.25% dydrocortisone, better than fluocortinbutylester and considerably better than bufexamac (Aertgeerts *et al.* 1985).

Assessors comment
The study does not support efficacy according to well-established use, but documents the traditional cutaneous use. Data regarding safety are lacking.

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

- Matricariae flos (cream with herbal preparation m)) vs. hydrocortisone cream 0.5%
- Matricariae flos (cream with herbal preparation m)) vs. placebo cream

The authors stated that after a 2-week treatment the cream with chamomile showed a mild superiority towards 0.5% hydrocortisone cream and a marginal difference compared to placebo (Patzelt-Wenczler and Ponce-Pöschl 2000).

Assessors comment
The study is not suitable to support WEU but supports traditional use on the skin in moderate atopic dermatitis.

Radiation skin reaction in breast cancer patients

The efficacy of a liquid extract (DER 2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= liquid extract m) 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 x 10 and 17 x 17 cm. Thirty

minutes before irradiation and at bed time the randomised preparation was administered above or 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 treatment with liquid extract m) the grade 1 reaction occurred slightly later. There were 7 patients with grade 2 reactions in the matricaria group compared to 13 patients under almond ointment treatment (Maiche *et al.* 1991).

Assessors comment
The study is too small to support WEU, the indication is not suitable for traditional herbal medicinal products.

Wound healing after proctologic operations

Marti (1977) documented the results of hip baths treated with a product containing herbal preparation l) after sphincterectomy due to anal fissures in 50 patients. The wound healing was normal. No safety concerns were reported.

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

Fifty patients (28 male, 22 female) suffered from different proctologic diseases (fistulae, perianal thrombosis, marisca) were postoperatively divided in two groups. All received 3 times per day a hip bath with a liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l). One group received additionally gauze compresses with liquid extract m) (DER 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 n) (DER 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 (Förster 1987).

Assessors comment
The study is not suitable for an efficacy assessment according to WEU criteria due to lacking controls, but does support the traditional use in wound healing of superficial wounds

Decubital ulcer / Ulcera crurum

One hundred eighty-two patients, 123 thereof with ulcera crurum (86 female, 37 male), 35 with decubital ulcers (16 female, 19 male), 24 toddlers with diaper rash (11 female, 13 male) (see children assessment) were treated with a liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l) and additionally with a dry extract (DER 11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= dry extract n), if infected. Clean ulcera crurum were treated with extract n). Ulcers with necroses, scabs or superinfection received dressings with extract l) several times a day and an extract (n) for the night. Therapeutic success was (very good or good) in decubital ulcers 60%, ulcera crurum 83% (Aertgeerts 1984).

4.3. 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. Three hundred sixty-two physicians were contacted to participate in an online system to document all prescriptions of Asteraceae containing extracts with the corresponding adverse drug reactions (ADR). One hundred seven physicians agreed to participate, 38 fulfilled the technical

requirements. Fifty-five per cent were general practitioners, 45% specialists (23% paediatricians, 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 18,830 patients no serious ADR was reported. In the analysis of the subgroup of seven physicians who also documented non serious ADR´s. Eleven non serious ADR´s for Asteraceae containing remedies occurred in 6,961 patients, 2 of these ADR´s were connected to preparations containing Matricaria flos. One 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 years old with an acute gastroenteritis. The second case was a gastralgia during an acute gastroenteritis of a 47 years 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%).

Oral use

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

- herbal tea (matricaria, vervain, licorice, fennel, balm mint)
- standardised extract of matricaria (*Matricaria recutita*), fennel (*Foeniculum vulgare*), and lemon balm (*Melissa officinalis*)
- liquid preparation containing apple pectin and matricaria fluid extract standardised 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 or as oral administration in children.

Cutaneous use

Aertgeerts (1984) reported on an observational study which included 182 patients who were treated with an ointment (containing liquid extract l)), 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). Twenty four infants (average age 7.5 month) were treated for diaper dermatitis, 123 patients (mean age 65 years) were treated for ulcus cruris and 35 patients (mean age 62 years) 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 (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (=liquid extract l)) 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 n)) in 54

patients with ulcera crurum. Seventeen of them suffered from an accompanying eczema. The evaluation followed the survey of the wounds (2 times per 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). Patients received 4% extract l) as compresses changed 4 times daily or 1 times extract n). Five patients dropped out due to superinfection, 7 patients were healed, 41 were better, 4 were unchanged, 2 worsened.

Peters (1988) observed the efficacy of a a cortisone free local treatment with a Matricariae 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 m) in treatment of diaper dermatitis was investigated (Viegas *et al.* 1996). Extract m) 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.

Assessors comment
The study is suitable to demonstrate the cutaneous medicinal use of extract m) 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 m) cream 3 times daily over 8 days. There were no adverse effects observed. The study does not allow any conclusion towards efficacy due to lacking controls.

4.4. 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. In section 4 literature data on trials are presented which are not sufficient to conclude for a well-established use, but which in summary do support the plausibility of the indications with respect to traditional use, which have been described in chapter 2.

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 already in 1978. 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 (Stiegelmeier 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 the local tolerance of inhalation - (see 5. Clinical safety). The open uncontrolled study of Troll and Patzelt-Wenczler (1990) tested steam inhalation versus mouth spray 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 and Menzel (1975), Carl and Emrich (1991) and Fidler *et al.* (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. This indication is supported by an open clinical study (Förster 1987) supporting the use of ethanolic extracts as hip bath after haemorrhoids ligature. In another clinical study Förster explored the different uses as hip bath, cream and ointment after different anal diseases: perianal thrombosis, mariscs and anal fistulae (Förster 1987).

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 sufficient to support WEU, due to lacking controls but cover the traditional plausibility in the relevant posologies.

Posologies defined in the monographs are based on the traditional use of existing products. Taking into account the accepted indications, data from clinical trials and the safety profile described in the following sections a duration of use of one week is justified.

5. Clinical Safety/Pharmacovigilance

5.1. 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 for two consecutive days (liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l)). Ten ml substitute was added to 450 ml boiled water. 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)

Ten patients suffering from COPD and 15 healthy probands were treated via inhalation with a liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l) in a dilution of 1:10 for 10 days. Before and 30 min after the steam inhalation vital capacity 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

Twenty four adult patients (14 female, 10 male) 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 standardised protocol using the same lyophilised 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 to *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*. Fifteen 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 *et al.* 2001).

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 out of 14 patients had a clinical history of immediate-type reactions to matricaria, in some cases life threatening. Concurrent sensitisation 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) resumed in her review regarding contact sensitisation from Compositae containing herbal remedies, that there was no difference between different preparations of *Matricaria recutita* and that the sensitisation/elicitation risk for dermatitis is low.

Cutaneous use

Aertgeerts published, that from 123 patients with ulcera crurum, treated with a liquid extract l (DER 1:4-4.5) 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 n (DER 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), 5 developed an eczema, which represents the risk of sensitisation in cases of chronic wounds from externa. Due to the observational quality of data, the differentiation between Matricariae flos and base components was not carried out. The observation of macerations (4 in decubitus and 3 in ulcera crurum) was probably due to the wound management and was not matricaria specific (Aertgeerts 1984).

Remme and de Witt (1984) studied the efficacy of a liquid extract (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l)) and a dry extract (DER 11-16:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= dry extract n)) in 54 patients with ulcera crurum. The patients received a medication with liquid extract l) or dry extract n) as compresses changed 4 times daily or 1 times extract n as ointment. Five patients dropped out due to superinfection, 7 patients healed, 41 got better, 4 were unchanged, 2 worsened, 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 (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l)) in a concentration of 0.5%. The evaluation followed 48 and 96 hours thereafter, 28 received the same test with undiluted extract l). Just one patient with a known allergy to matricaria - even when she collected them - reacted with a type IV allergy to undiluted extract l), but not towards diluted extract l). The study cannot be used to assess a sensitisation potential, because the prophetic testing is lacking, but supports a low allergic risk of Matricariae 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 (DER 1:4-4.5) extraction solvent: ethanol 38.5% m/m (containing 1.36% sodium acetate trihydrate, 0.45% sodium ascorbate and 0.41% sodium hydroxide) (= liquid extract l)) in a concentration of 0.5%, a liquid extract (DER 2.7-5.5:1), extraction solvent: ethanol 95.4% V/V (containing 0.22% sodium acetate, 0.12% sodium hydroxide) (= liquid extract m)) or a dry extract (=extract n))(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 sensitisation potential, but supports a low allergic risk of Matricariae flos.

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

Twenty 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. Fifteen (43%) of 35 patients tested positively to 1 or more spots on the thin-layer chromatogram, with many individual reaction patterns.

5.2. Patient exposure

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

Publication	**cutaneous use n=persons**	**Oral use n=persons**	**Inhalation n=persons**	**Gargling/rinsing n=persons**
Adults				
Aertgeerts 1984	158			
Aertgeerts *et al.* 1985	161			
Amsterdam 2009		28 GAD US		
Carl and Emrich 1991				98
Fidler *et al.* 1996				81
Förster 1987	50			
Jablonska and Rudzki 1996	540 contact eczema			
Kerscher 1992	24			
Lauber 1987			34 risk (bronchial hyper-reagibility, obstructive lung disease	
Maiche *et al.* 1991	25 female			
Marti 1977	50 anal fissures, hip bath			

Nasemann 1975	38			
Nasemann and Menzel 1975	78			27
Patzelt 2000	72			
Peters 1987	50 neurodermitis			
Remme and de Witt 1984	54 ulcera crurum			
Rudzki and Jablonska 2000	982 type IV sensitisations			
Sauer 1990			53 sinusitis maxillaris	
Schmidt 1975			10 chronic obstructive bronchitis	
Stiegelmeyer 1978		104 unspecific stomach complaints		
Troll and Patzelt-Wenczler 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 – 5.5 years De la Motte *et al.* 1997		79 combination		
Children 1 month – 6 years Becker *et al.* 2006		121 combination		
Infants Aertgeerts 1984	24 monopreparation			
Infants Weizman *et al.* 1993		34 combination		
Infants 21 days – 60 days Savino *et al.* 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 *et al.* 2010	76 no differentiation			
Facchinetti *et al.* 2012	250 no differentiation predominantly oral			
Forster *et al.* 2006	65 no differentiation			
Holst *et al.* 2011		76		
Moussally *et al.* 2009		122		

Moussally and Bérard 2012		20 preterm birth, part of the data above		
Nordeng and Havnen 2004		13		
Sum: 1,153 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 oral 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 *et al.* (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.

5.3. Adverse events, 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 from literature and national pharmacovigilance data bases (see also 4.4, 4.7 and 4.9). The majority of data is referring to herbal preparations of *Matricaria recutita,* flos. Corresponding sections of the monograph of Matricaria oil have been adapted to this data.

Case reports

Subiza *et al.* (1989) reported about an 8 years 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 dyspnoea and wheezing. His mother tried to relieve the symptoms with a cup of matricaria tea. Several minutes later the patient deteriorated with dyspnoea, loss of consciousness and shock. After medical intervention he could be stabilised. As cause an IgE mediated immunologic reaction potentially cross reacting with the known mugwort allergy could be identified.

Scala (2006) reported on a 20 years 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 years old woman 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 oedema, tachycardia, hypotension with loss of cardiac sounds in cardiotocography. 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 about a 69 years old male, 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 anti-allergic treatment the symptoms removed. The medical history revealed a seasonal rhinitis. Skinprick tests to aeroallergens showed a reaction to ragweed (13 mM), 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 a 35 years old atopic female, who had a known ragweed hay fever. After several sips of the tea, she developed abdominal cramps, 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 anti-allergic treatment with diphenhydramine and cortison the symptoms removed.

5.4. Laboratory findings

Laboratory data were not published.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

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). One hundred seven physicians agreed to participate, 38 fulfilled the technical requirements, 55% were general practitioners, 45% specialists (23% paediatricians, 11% internal medicine, 11% others). From September 2004-September 2006 50,115 patients were documented, who received 199,9387 prescriptions for 360,488 drugs and 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 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. 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, 2 of these ADR´s were connected to preparations containing Matricaria flos One 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 years old with an acute gastroenteritis. The second case was a gastralgia during an acute gastroenteritis of a 47 years 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.

Oral 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, randomised, 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, balm mint) or placebo tea (glucose, flavouring). Each infant was offered treatment with every bout of colic, up to 150 ml/dose, no more than 3 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 randomised, double-blind, placebo-controlled trial of 93 breastfed term born colicky infants (21 days to 60 days) compared a standardised extract of chamomile (*Matricaria 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, randomised, controlled multicentre study, 79 children from the ages of 6 months to 5.5 years who had acute, non-complicated diarrhoea were given either a liquid preparation containing apple pectin and matricaria liquid extract standardised 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 diarrhoea more frequently than did the placebo (p=0.05) (De La Motte *et al.* 1997).

A combination product (apple pectine and matricaria liquid extract) was investigated in a double-blind, randomised trial in children from 6 months to 6 years of age with unspecific diarrhoea (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 multicentre, randomised, double-blind, placebo-controlled parallel study of 255 children who had acute diarrhoea demonstrated that the 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 l) as a washing and thereafter extract n) ointment. Irritation of the skin was observed in 2 infants (Aertgeerts 1984).

Fifty five toddlers (31 female, 24 male, age range 2 weeks – 36 months) with diaper rash were treated at every diaper change with extract n) cream. In 2 children a desquamation if the skin, in two children a reddening of the skin was noted (Viegas *et al.* 1996).

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

Assessors comment

Due to the long term use and the lack of safety concerns the publication of KOOP Phytopharmaka (Dorsch et al. 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.

5.5.2. Drug Interactions and other forms of interaction

Case reports

Segal and Pilote (2006) reported on a 70 years 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 day per week; 6 mg 4 day per week) amiodarone, digoxin, synthroid, alendronate metoprolol and a calcium-vitamin D-supplement. An infection of the upper respiratory tract was diagnosed and she was discharged without further medication. Five days later she was suffering from the same symptoms as well as dyspnoea on exertion, bipedial oedema, 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 stabilised and discharged. On further questioning she admitted to use 2 teaspoons full of a matricaria based skin lotion to treat her pedal oedema 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 metabolised 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 3 cases of patients with cadaveric renal allografts under stable immunosuppression with cyclosporine (metabolised via CYP3A4) and mycophenolate mofetil (MMF)(metabolised via glucuronisation) changing under fluid excess via herbal teas. Two of the case reports were associated with matricaria tea.

Case A: A 48 years old woman having cyclosporine trough levels of 110-140 µg/l under 2 times 110 mg per day, developed gradually declining trough levels down to 80 µg/l under increasing doses of cyclosporine (2 times 170 mg per day). 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 water the trough levels of cyclosporine increased, despite reduced doses (2 times 150 mg per day). A reexposition to the former tea led to decreasing trough levels within 2 weeks.

Case B: A 37 years 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 times 75 mg per day), reported drinking at least 1.5 l of matricaria tea per 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 times 100 mg per day).

Assessors comment

The case reports are inconsistent. Segal and Pilote argue the coumarin 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 standardised 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."

5.5.3. Fertility, 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. Three hundred thirty-four (57.8%) used at least one herbal product, 76 used matricaria. For matricaria tea, not exceeding the use as a nutrient, there was no documented risk (Holst *et al.* 2011).

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 any 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. Three thousand seven hundred seventy-four 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% of them 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 above mentioned studies with large numbers of pregnant women showed no risk for the use of 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 reports include severe anaphylactic reactions, 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 herbal tea.

Since data regarding the cutaneous use of matricaria containing preparations during lactation are not available the use during pregnancy and lactation is not recommended. Nevertheless, sore nipples are a common problem. Therefore, if applicable (e. g. for herbal tea) the following text should be included under pregnancy and lactation to prevent sensitisation of breastfed babies: "Before nursing the baby the nipples should be cleaned from matricaria containing products to prevent a sensitisation of the baby."

5.6. Overall conclusions on clinical safety

The clinical safety of *Matricaria recutita* containing preparations is good. The main risk is a sensitisation 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 in the monograph.

To prevent sensitisation of breastfed babies a note has to be introduced, if appropriate in the section on pregnancy, lactation and fertility:

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

Other specific risks for children of any age group are not deductible. Pregnant women may use herbal tea, for all other preparations there is a lack of data. Therefore for all other herbal preparations mentioned in the monograph the use during pregnancy and lactation is not recommended.

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."

6. Overall conclusions (benefit-risk assessment)

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 attests to that.

Only one clinical study of good quality according to current standards has been identified (Amsterdam *et al.* 2009). As the studied indication (generalised 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 Matricariae flos can be accepted for the following indications for adolescents, adults and elderly. The use in children of different age groups for distinct indications was acceptable for few herbal preparations (a), e), g), h), k), l), m), o)), because data were available and safety has been sufficiently demonstrated.

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

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

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

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.

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

For Matricariae aetheroleum no sufficient clinical evidence could be identified except observational data from Marti (1977). Based on pharmacological data and medicinal products authorised or registered in the EU the traditional use as bath additive 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.

Relevant sections of the monograph on Matricaria oil have been aligned to the monograph on Matricariae flos if appropriate.

Safety

The main safety issue is sensitisation regarding allergies towards Asteraceae. Jeschke *et al.* (2009) published data from 1,602 patients where the reported rate of allergies was 0.12%. The labeling is adapted accordingly.

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 for the majority of herbal preparations not recommended because absence of sufficient data. Only herbal tea can be recommended in pregnant women and during breast feeding.

Risk Benefit assessment

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

A European Union list entry is not established due to lack of sufficient data on genotoxicity.

Annex

List of references