EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Achillea millefolium* L., herba

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Achillea millefolium* L., herba
Herbal preparation(s)	Comminuted herbal substance. Expressed juice from fresh herb (DER 1:0.6-0.9). Liquid extract (DER 1:1) extraction solvent ethanol 25% (V/V). Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 31.5% (V/V). Tincture (ratio of herbal substance to extraction solvent: 1:5), extraction solvent ethanol 45% (V/V).
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use or for infusion preparation for cutaneous use. Herbal preparations in liquid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Definition:

The whole or cut dried flowering tops of yarrow, *Achillea millefolium.*

This definition can be found in:

- European Pharmacopoeia 7th ed. (2010) Yarrow,
- Extra Pharmacopoeia Martindale XXV. Edition (Todd 1976),
- Herbal Medicines (Newal et al. 1996), (Barnes et al. 2007),
- WHO Monographs (Volume 4, 2009),
- ESCOP Monographs (Supplement 2009).

Fresh or dried aerial (above ground) part collected during the flowering season of *Achillea millefolium.*

This definition can be found in:

- Pharmacopoeia Hungarica Editio VI. Tomus III, 1967,
- Hagers Handbuch der Pharmazeutischen Praxis (Kern 1969),
- German Commission E Monograph 1990,
- British Herbal Pharmacopoeia 1996 (dried aerial parts),
- British Herbal Compendium (dried aerial parts) (Volume 1, Bradley 1992),
- WHO Monographs (Volume 4, 2009),
- ESCOP Monographs (Supplement 2009).

Assessor's comment: The MLWP decided to use the definition of the European Pharmacopoeia monograph for Yarrow.

- Herbal preparation(s)
  - Communited herbal substance as infusion for tea preparation (Augustin et al. 1948, Todd 1967, BHP 1974, Rácz et al. 1984, German Commission E monograph 1990, Blumenthal et al. 1998, Wren 1988, Bisset 1994, Newal et al. 1996, Hänsel et al. 1992, Bradley 1992)
  - Expressed juice (1:1) from fresh herb (Blumenthal et al. 1998, Hänsel et al. 1992)
  - Liquid extract (1:1), extraction solvent: ethanol 25% (V/V) (Wren 1988, Bradley 1992, Newal et al. 1996, BHP 1974)
  - Tincture (1:5) extraction solvent: ethanol 45% (V/V) (Bradley 1992, Newal et al. 1996, BHP 1974)
- 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.

Millefolii herba is a frequent component of combinations mainly for mild cramp-like, gastrointestinal complaints, catarrh and loss of appetite.

Phytochemical characteristics

Achillea millefolium L. s.l. is a cytogenetically, morphologically, and chemically polymorphic aggregate. The genus *Achillea* consists of about 140 perennial herbs native in the Northern hemisphere.

Principal components of the herbal substance

Yarrow contains 3-4% condensed and hydrolysable tannins; 0.3-1.4% volatile oils, mostly linalool, borneol, camphor, β-caryophyllene, 1,8-cineole, and sesquiterpene lactones composed of guaianolides, mainly achillicin (a proazulene), achillin, leucodin, and germacranolides (dihydroparthenolide, achillifolin, millefin); flavonoids (apigenin, luteolin, isorhamnetin, rutin); amino acids (alanine, histidine, leucine, lysine); fatty acids (linoleic, palmitic, oleic); phenolic acids (caffeic, salicylic); vitamins (ascorbic acid, folic acid); alkaloids and bases (achiceine, achilleine, betaine, choline); alkanes (tricosane); polyacetylenes; saponins; sterols (β-sitosterol); sugars (dextrose, glucose, mannitol, sucrose); and coumarins (Blumenthal et al. 2000).

According to the literature the pharmacological effects are mainly due to the essential oil, proazulenes and other sesquiterpene lactones, phenolic compounds such as dicaffeoylquinic acids and flavonoids. However, according to the two below mentioned articles these components can be found in very different quantities in the various plant materials.

Benedek et al. (2007 (a)) developed a SPE-HPLC/UV method that allows quantification of the phenolic constituents in the different taxa in order to evaluate their contribution to the chemotaxonomy of European taxa of the *A. millefolium* group. The investigated species displayed differences in the quantitative and qualitative composition of phenolic acids and flavonoids. Hence, they seem to be of chemotaxonomic significance, especially for the distinction of the diploid taxa. Combining the obtained results with the data of the sesquiterpene analyses they can give a comprehensive insight into the distribution of those pharmacologically relevant plant constituents in the *A. millefolium* group.

In their study Benedek et al. (2008) revealed that the quality of 40 commercial drug samples was very heterogenous and only 50% of the samples met the standards of the European Pharmacopoeia.

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

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination.
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Plus in combination.
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination.
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination.
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
Germany	☒ MA 5	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	"Healing products".
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products.
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination.
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products.
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

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

Table I. Products on the market as provided by the Member states.

Active substance, pharmaceutical form	**Indication**	**Posology**	**Legal status**
20 g extract from Millefolii herba (1:5), 80 g ethanol (29% V/V) oral solution (HU).	Treatment of inflammatory disorders of the stomach and the colon. Appetizer.	3x30 drops daily in a small volume of fluid, taken before meals.	Since 1995 "Healing products".
190 mg finely chopped *Millefolii herba*, coated tablet (HU).	Digestive, spasmolytic, appetizer.	3x3-4 coated tablets (corresponding to 3x570-760 mg herbal substance).	Since 1996 "Healing products"
Tincture from *Millefolii herba* (1:5), extraction solvent: ethanol 31.5% V/V, oral liquid (DE).	Digestive complaints like mild spasms in the gastro-intestinal tract, loss of appetite.	4 times daily 4.3 ml (=4.2 g) liquid containing 100% tincture.	At least since 1976, well-established use.
Expressed juice (1:0.65-0.85) from fresh *Millefolii herba*, oral liquid (DE).	Digestive complaints like mild spasms in the gastro-intestinal tract, loss of appetite.	3 times daily 5 ml liquid containing 100% expressed juice.	At least since 1976, well-established use.
Expressed juice (1:0.84-0.93) from fresh *Millefolii herba*, oral liquid (DE).	Digestive complaints like mild spasms in the gastro-intestinal tract, loss of appetite.	2 times daily 10 ml liquid containing 100% expressed juice.	At least since 1990 (already authorised in the former GDR), well-established use.
Millefolii herba (CZ).	Oral use: for symptomatic treatment of mild gastro-intestinal complaints, and loss of appetite. Oromucosal use: for symptomatic treatment of minor inflammations in the mouth and throat. Topical use: for treatment of minor skin inflammations several times daily (as a bath or poultice).	For oral, oromucosal and topical use. For oral use: 1.5 g (1 teaspoon)/250 ml of boiling water/15 minutes 2– times daily. For oromucosal and topical use: 3 to 4.5 g (2–3 teaspoons)/250 ml of boiling water/15 minutes.	1997.
Herbal substance (*Millefolii herba*) as herbal tea (PL).	Traditional herbal medicinal product for treatment loss of appetite and dyspeptic complaints (mild, spastic gastrointestinal discomfort). Topical use: small superficial epidermal excoriation.	Oral use: (infusion) 3.5 g of herbal substance in ½ glass of bolding water 2–3 times daily. Topical use: Infusion should be prepared the same way.	More than 30 years.

1.3. Search and assessment methodology

The assessment report of *Millefolii herba* is based on the following literature resources:

- Monographs: ESCOP Monographs (Supplement 2009), WHO Monographs on Selected Medicinal Plants (Volume 4 2009), Hagers Handbuch (Hansel et al. 1992), Expanded Commission E Monograph (Blumenthal et al. 2000).
- Articles and references retrieved from data bases (Pubmed, Toxnet) or internet sources (e.g. Google) until the end of 2009. The term *Achillea millefolium* was searched.

Articles and data that were found to be relevant for assessment are included in the list of references.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

According to Blumenthal et al. (2000), yarrow has been used as medicine by many cultures for hundreds of years (Budavari 1996; Zeylstra 1997). Its English common name is a corruption of the Anglo-Saxon name *gearwe*; the Dutch, *yerw*. The genus name *Achillea* may derive from Achilles of the Greek mythology, who was fabled to have had his wounds treated by topical use of the herb. The species name *millefolium* derives from the many segments of its foliage. The ancient Europeans called it *Herba Militaris*, the military herb – an ointment made from it was used as vulnerary drug on battle wounds. Yarrow flower was formerly official in the United States Pharmacopoeia. Additionally, it is listed in the Indian Ayurvedic Pharmacopoeia for fevers and wound healing (Karnick 1994).

European National pharmacopoeial monographs:

- Hungarian Pharmacopoeia 6th Edition Volume III (1967),
- Extra Pharmacopoeia Martindale Twenty-fifth edition (1967),
- British Herbal Pharmacopoeia (BHP) 1974, 1996,
- Polish Herbal Compendium (1978),
- German Pharmacopoeia (1997),
- Austrian, Czech, French, Romanian Pharmacopoeias (mentioned by Newal et al. 1996).

Other monographs:

- Hungarian Herbal Drugs (Augustin et al. 1948),
- German Commission E monograph (1990),
- Hagers Handbuch (Kern et al. 1969, Hansel et al. 1992),
- Potter's New Cyclopaedia of Botanical Drugs and Preparations (Wren 1988).

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

Evidence regarding the indication/traditional use

In Belgium (cited in Bradley 1992):

Circulaire No. 367 of July 1991: Traditionally used topically as soothing antipruriginous application for dermatological affection.

In France (cited in Bradley 1992):

Bulletin Officiel No.90/22 bis: Achillée millefeuille, sommité fleurie.

Taken orally: traditionally used in symptomatic treatment digestive disorders such as epigastric distension; sluggishness of digestion; belching; flatulence as adjuvant treatment for painful component of spasmodic colitis.

Traditionally used topically as soothing and antipruriginous application for dermatological ailments, as protective treatment for cracks, grazes, chaps and against insect bites.

In Germany:

As aromatic, somatic, adstringent, choleretic, in problems of menstruation, in bleeding haemorrhoids, varicose veins, as diuretic in hypertension, diaphoretic, liver problems, emmenagogue, abortifacient, in pertussis, lung tuberculosis, haematoma, as an infusion or expressed juice from fresh herb for spring-cure. Externally it is used for healing wounds and ulcers similarly as chamomile (Kern et al. 1969).

Internally: loss of appetite; dyspeptic complaints such as mild, spasmodic disturbances in the gastrointestinal region. In hip baths: painful, cramp-like conditions of psychosomatic origin (in the lower part of female pelvis) (German Commission E monograph 1990, Hänsel et al. 1992).

Gastrointestinal complaints (inflammation, diarrhoea, flatulence, cramps), as bitter aromatic for loss of appetite, and for stimulation of bile secretion. Externally: inflammation of the skin and mucous membranes, for healing wounds. In folk medicine, the drug is often employed as haemostyptic, e.g. for bleeding from haemorrhoids, and in problems of menstruation and to treat perspiration (baths) (Bisset 1994, Hänsel et al. 1992).

The use of Millefolii herba in case of dysmenorrhoea is mentioned already in the Madaus handbook (1938) until now, in recent editions of handbooks on phytotherapy (e.g. Fintelmann and Weiss 2002). In this reference also the use of the infusion (1 spoon of comminuted herbal substance per cup, several times a day) is mentioned.

In Romania (Rácz et al. 1984):

It is used for the inflammation of the mucous membrane of the stomach, gastric-, duodenal ulcer, catarrh of the colon. It is used externally for bathing of babies, and of patients with eczema as well as rinse in parodonditis.

In the United Kingdom:

Diaphoretic, stimulant, and haemostatic (Todd 1967).

Indications: feverish conditions, common cold; digestive complaints. Other uses: loss of appetite, hypertension, menstrual irregularities. It is used topically for slow-healing wounds and skin inflammation (Newal et al. 1992, Bradley 1992, British Herbal Pharmacopoeia 1974, Wren 1988, first published in 1907).

In Hungary:

Millefolii herba belongs to the bitter substances, because it stimulates the digestive system and metabolism. In folk medicine, it has been used in female diseases, especially in the climacteric period; the drug is often employed as a haemostyptic in bleedings from the intestine, uterus, lung or nose (Augustin et al. 1948).

<u>The proposed indications for the monograph:</u>

Indications based on products on the markets for more than 30 years:

- Traditional herbal medicinal product used for temporary loss of appetite (*indication 1)*).
- Traditional herbal medicinal product for symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence (*indication 2)*).
- Traditional herbal medicinal product for treatment of small superficial wound.(*indication 4)*)

Indications based on literature:

- For symptomatic treatment of minor spasm associated with menstrual periods (*indication 3)*).

Assessor's comment: During the consultation period indication 3 in the form of hip baths was recommended by an interested party based on the reference of Weiss RF 1982. The working party questioned the plausibility of this indication. Spasmolytic, anti-inflammatory or analgesic effect cannot be expected through cutaneous use. Only the warm water may have some spasmolytic effect. Moreover incomplete usage data such as the duration of treatment lead to the decision not to accept this form of administration.

Evidence regarding specified substances/preparations

Herbal substance:

Not applicable.

Herbal preparations:

In the literature:

- Comminuted herbal substance as infusion for tea preparation (Kern et al. 1969, Hansel et al. 1992, BHP 1974, 1983, Augustin et al. 1948, Rácz et al. 1984, German Commission E monograph 1990, Wren 1988, Bisset 1994, Newal et al. 1996, Bradley 1992, Bisset 1994, Newal et al. 1996)
- Liquid extract (DER: 1:1), extraction solvent: ethanol 25% (V/V) (BHP 1974, Wren 1988, Bradley 1992, Newal et al. 1996)
- Tincture (ratio of herbal substance to extraction solvent: 1:5)**,** extraction solvent: ethanol 45% (V/V) (BHP 1974, Bradley 1992, Newal et al. 1996)

Products on the market for more than thirty years:

- Comminuted herbal substance
- Expressed juice from fresh herb (DER 1:0.65-0.85)
- Expressed juice from fresh herb (DER 1:0.84-0.93)
- Tincture (ratio of herbal substance to extraction solvent: 1:5), extraction solvent ethanol 31.5% (V/V).

Assessor's comment: The two expressed juices are combined in the monograph:

Expressed juice from fresh herb (DER 1:0.6-0.9).

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

Indication 1) and 2):

Comminuted herbal substance as infusion for tea preparation

Three times daily: 2-4 g (Todd 1967, Bradley 1992, Hänsel et al. 1992).

Daily dose: 4.5 g of yarrow herb (German Commission E monograph 1990, Bisset 1994).

Wording of the package insert, from the German Standard Licence:

Hot water (ca. 150 ml) is poured over two teaspoonfuls (2-4 g) of yarrow and after 10 minutes passed through a tea strainer. Unless otherwise prescribed, a cup of freshly prepared infusion is taken when still warm three or four times a day between meals (in Bisset 1994, Hänsel et al. 1992).

Single dose: 1.5 g (Kern 1969).

Herbal tea: 3.5 g of herbal substance as infusion in ½ glass of boiling water 2-3 times daily (products on the market for more than 30 years in Poland).

Expressed juice from fresh herb

DER 1:0.6-0.9; 3 times daily 5 ml liquid containing 100% expressed juice (product on the market for more than 30 years).

DER 1:0.8–1; 2 times daily 10 ml liquid containing 100% expressed juice (product on the market for more than 30 years).

Assessor's comment: The two expressed juices are combined in the monograph:

Expressed juice (DER: 1:0.6-0.9) from fresh herb 5-10 ml twice or three times daily.

Liquid extract (DER: 1:1), extraction solvent: ethanol 25% (V/V): 2-4ml three times daily (Wren 1988, Bradley 1992, Newal et al. 1996, BHP 1974).

Tincture (ratio of herbal substance to extraction solvent: 1:5), extraction solvent: ethanol 45% (V/V): 2-4 ml three times daily (Bradley 1992, Newal et al. 1996, BHP1974).

Tincture (ratio of herbal substance to extraction solvent: 1:5), extraction solvent: ethanol 31.5% (V/V) 4 times daily 4.3 ml (=4.2 g) (products on the market for more than 30 years).

Indication 3):

One spoon of comminuted herbal substance per cup, as infusion, several times a day (Madaus 1938, Fintelmann and Weiss 2002).

Indication 4):

Herbal substance as herbal tea (infusion) 3.5 g of herbal substance in ½ glass of boiling water 2–3 times daily (products on the market for more than 30 years in Poland).

The posology in the monograph

Adolescents, adults and elderly.

Single dose.

Oral use:

Indications 1) and 2):

a) Herbal tea: 2-4g of the comminuted herbal substance in 250 ml boiling water as a herbal infusion three or four times a day between meals.

b) Expressed juice 5-10 ml twice or three times daily.

c) Liquid extract 2-4 ml three times daily.

d) Tincture extraction solvent ethanol 45% (V/V) 2–4 ml three times daily.

e) Tincture extraction solvent ethanol 31.5% (V/V) 4.3 ml (=4.2 g) four times daily.

For the indication "loss of appetite" the liquid preparations are to be taken 30 minutes before meals.

Indication 3):

Herbal tea: 1-2 g of the comminuted herbal substance in 250 ml boiling water as a herbal infusion 2-3 times daily.

Cutaneous use:

Indication 4):

Comminuted herbal substance for infusion preparation for cutaneous use: 3.5 g of the comminuted herbal substance in 250 ml water 2-3 times daily.

The use in children under 12 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').

Assessor's comment: The use of the comminuted herbal substance by adolescents was accepted taking into consideration that Millefoii flos liquid extract has been used traditionally by adolescents for more than 30 years. There are no safety concerns since a herbal tea preparation contains assumingly a similar or rather lower amount of ingredients compared to a liquid extract prepared with liquor vine: ethanol 96% (V/V) 91:9 (m/m). The cutaneous use for adolescents can also be considered as safe.

Duration of use

Indications 1) and 2):

If the symptoms persist more than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indications 3 and 4):

If the symptoms persist more than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Method of administration

Indications 1), 2) and 3):

Oral use.

Indication 4):

Cutaneous use: to be applied to the affected area in a form of impregnated dressing.

3. Non-Clinical Data

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

***In vitro* studies**

- Anti-inflammatory activity

An extract of yarrow herb, prepared as 0.2 mg/ml of a lyophilized cold water extract, produced 41±2% inhibition of platelet activating factor (PAF)-induced exocytosis of elastase from human neutrophils.

The same extract (0.2 mg/ml) showed 21±2% activity in a test for inhibition of the biosynthesis of prostaglandins from ^{14}C-arachidonic acid (Tunón et al. 1995).

As various proteases, for instance human neutrophil elastase (HNE) and matrix metalloproteinases (MMP-2 and -9), are associated with the inflammatory process, the aim of the study was to test a methanolic [20% (V/V)] lyophilized extract (DER:2.75:1) of powdered **aerial parts of** *Achillea millefolium* L. s.l in *in vitro*-protease inhibition assays for understanding the mechanisms of anti-inflammatory action. Furthermore, two fractions enriched in flavonoids and dicaffeoylquinic acids (DCQAs), respectively, were also tested in order to evaluate their contribution to the antiphlogistic activity of the plant. The extract and the flavonoid fraction inhibited HNE showing IC_{50} values of approximately 20 microgram/ml, whereas the DCQA fraction was less active (IC_{50}=72 microgram/ml). The inhibitory activity on MMP-2 and -9 was observed at IC_{50} values from 600 to 800 microgram/ml, whereas the DCQA fraction showed stronger effects than the flavonoid fraction and the extract. The authors concluded that the *in vitro* antiphlogistic activity of *Achillea* was at least partially mediated by inhibition of HNE and MMP-2 and -9 (Benedek et al. 2007 (b)).

An inhibitory effect of the water soluble fraction of a hydro-alcoholic extract of *Achillea millefolium* was measured with the value of IC_{50}=1.25 mg/ml on soybean 15-lipoxygenase assay (IC_{50}=concentration which gave 50% inhibition) (Trouillas et al. 2003).

- Anti-oxidant effects

An anti-oxidant activity of the water-soluble fraction from a hydro-alcoholic extract of *Achillea millefolium* was demonstrated in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging test (IC_{50}=0.13 mg/ml), in the hydroxyl radical scavenging test IC_{50}=0.26 mg/ml) and in the superoxide radical scavenging test (IC_{50}=0.82 mg/ml). Other 15 plant extracts were also tested, and the antioxidant effects were correlated with the total amount of phenolic compounds contained in the extracts (Trouillas et al. 2003).

Infusions of pulverized **flower heads** of various *Achillea* (Asteraceae) species protected human erythrocytes and leucocytes against hydrogen peroxide-induced oxidative damage. This was shown by increased catalase, superoxid dismutase and glutation peroxidase activities, as well as by reduced glutathione content of the cells and decrease in lipid peroxidation (Konyalioglu and Karamenderes 2005).

Steam-distilled and non-distilled plant material from yarrow *(A. millefolium* L*.)* was extracted with solvents of different polarity and the resulting fractions were evaluated for their radical scavenging activity by the DPPH, NBT/hypoxanthine superoxide, and $^{\bullet}$OH/luminol chemiluminescence methods and for their antioxidant activity by the β-carotene blenching test. The total phenolic content was determined by the Folin-Ciocalteu method. Both, a remarkably high phenolic content and radical scavenging activities were found for the ethyl acetate and dichloromethane fractions. In general, the distilled plant material was found to exhibit a higher phenolic content as well as antioxidant and radical scavenging activities than the non-distilled material (Parejo et al. 2002)

The *in vitro* antioxidant activities of the essential oil and methanol extracts of *Achillea millefolium* subsp. millefolium Afan. were investigated by Candan et al. GC-MS analysis of the essential oil resulted in the identification of 36 compounds, constituting 90.8% of the total oil. Eucalyptol, camphor, alpha-terpineol, beta-pinene, and borneol were the principal components comprising 60.7% of the oil. The oil strongly reduced the diphenylpicrylhydrazyl radical (IC_{50}=1.56 micro g/ml) and exhibited the hydroxyl radical scavenging effect in the Fe(3+)-EDTA-H(2)O(2) deoxyribose system (IC_{50} =2.7 micro g/ml). It also inhibited the non-enzymatic lipid peroxidation of rat liver homogenate (IC_{50} =13.5 micro g/ml). The polar phase of the extract showed antioxidant activity (Candan et al. 2003).

- Anti-proliferative activity

The above mentioned water-soluble fraction from a hydro-alcoholic extract of *Achillea millefolium* showed a anti-proliferative effect on B16 mouse melanoma cells after two days of growth. It inhibited cell proliferation at 0.05-0.1mg/ml concentration (Trouillas et al. 2003).

The mechanism of anti-tumour activity of the flavonoid casticin, derived from *Achillea millefolium* was studied by Haidara K. et al. (2006). Casticin anti-tumour activity results in cell growth arrest in G2/M and in apoptotic death. As a tubulin-binding agent (TBA), casticin induces p21, which in turn inhibits Cdk1. Moreover, casticin appears to downregulate cyclin A. These observations could explain casticin induced G2/M arrest. Following casticin exposure, Bcl-2 depletion occurs in cancer cells, and a sub-G1 accumulation occurs in the cell cycle. Moreover, following a transient transfection with Bcl-2 MN1, cells are resistant to casticin. According to the authors a number of features suggest that casticin could be important in cancer therapy. Indeed, Pgp overexpressing cells are not resistant to casticin, and its cell killing effect is observed even in p53 mutant or null cell lines (Haidara et al. 2006).

The antiproliferative activities of n-hexane, chloroform, aqueous-methanol and aqueous extracts of the **aerial parts** of the *Achillea millefolium* aggregate on three human tumour cell lines were investigated by means of MTT assays. The chloroform-soluble extract exerted high tumour cell proliferation inhibitory activities on HeLa and MCF-7 cells, and a moderate effect on A431 cells; accordingly, it was subjected to detailed bioactivity-guided fractionation. As a result of the multistep chromatographic purifications (VLC, CPC, PLC, gel filtration), five flavonoids (apigenin, luteolin, centaureidin, casticin and artemetin) and five sesquiterpenoids (paulitin, isopaulitin, psilostachyin C, desacetylmatricarin and sintenin) were isolated and identified by spectroscopic methods. The antiproliferative assay demonstrated that centaureidin is the most effective constituent of the aerial parts of yarrow: high cell growth inhibitory activities were observed especially on HeLa (IC_{50}=0.0819 microm) and MCF-7 (IC_{50}=0.1250 microm) cells. Casticin and paulitin were also highly effective against all three tumour cell lines (IC_{50}=1.286-4.76 microm), while apigenin, luteolin and isopaulitin proved to be moderately active (IC_{50} =6.95-32.88 microm). Artemetin, psilostachyin C, desacetylmatricarin and sintenin did not display antiproliferative effects against these cell lines (Csupor-Löffler et al. 2009).

A lyophilized decoction (approx. 5:1) from yarrow (*Achillea millefolium* L.*)* was evaluated for anti-hepatoma activity (cytotoxicity) on five human liver cancer cell lines; at 2mg/ml the average inhibition of proliferation was 55% on non-hepatitis B virus cell lines and 20% on hepatitis B virus cell lines (Lin et al. 2002 - abstract).

- Oestrogenic activity

Dry methanolic and 10%-methanolic extracts of the aerial parts of *A. millefolium* showed oestrogenic activity in transgenic MCF-7 cells. The lowest effective concentrations were 8.57×10^{-5} mg/ml and 2.8×10^{-4} mg/ml respectively ($p<0.01$). Positive oestrogenic effects were also observed with compounds isolated from the 10%-methanolic extract: apigenin (2.5×10^{-4} mg/ml) luteolin (8.9×10^{-3} mg/ml) and their 7-O–glucosides (3.9×10^{-5} mg/ml and 3.4×10^{-5} mg/ml respectively). Apigenin and luteolin, the most important estrogenic compounds among those tested, were studied for their ability to activate alpha or beta oestrogen receptors (ERalpha, ERbeta) using transiently transfected cells. On the basis of their results the authors suggest that apigenin can stimulate ERs-dependent biological pathways, although with a smaller potency as compared with the endogenous hormone. Both receptors, alpha and beta, can be activated by apigenin. Luteolin seems to have a very slight effect on beta receptors and does not seem to activate alpha receptors at all. However the role of apigenin in emmenagogic effects of *A. millefolium* – as traditionally reported- can not be defined on this basis (Innocenti et al. 2007).

- Antispasmodic activity

Antispasmodic activity on isolated rabbit intestine has been documented for flavonoid-containing fraction of the **aerial parts** of yarrow (Hoerhammer 1961).

The spasmolytic activity of a flavonoid fraction of a commercial sample of yarrow (*Achillea millefolium* L. s.l), its main flavonoids as well as quercetin and two flavonoid metabolites were investigated on isolated guinea-pig ilea. The aglycones quercetin, luteolin and apigenin exhibited the highest antispasmodic activities with IC_{50} values of 7.8 µmol/L, 9.8 µmol/L and 12.5 µmol/L, respectively. Rutin and the flavonoid metabolites homovanillic and homoproto-catechuic acid showed no significant effects on contractility of the terminal ilea. From the results on the spasmolytic activity of the flavonoid fraction, the glycosides and respective aglycones it was concluded by the author that in tea prepared from yarrow the concentration of flavonoids high enough to exert a spasmolytic effect in gut, which is mainly caused by blockade of the calcium inward current, but additionally also by mediator-antagonistic effects (Lemmens-Gruber et al. 2006).

In isolated rabbit jejunum preparations, a 70%-methanolic extract of the **aerial parts** of *Achillea millefolium* (DER: 5.5:1) caused a concentration-dependent (0.3-10 mg/mL) relaxation of both spontaneous and K^+-induced contractions as well as shifting the Ca^{++} concentration-response curves to the right, similar to that caused by verapamil (Yaeesh et al. 2006).

- Choleretic effect

Benedek et al. (2006) investigated the choleretic effect in the isolated perfused rat liver (IPRL) of a fraction from a 20% methanolic extract of **the aerial part of yarrow** enriched in dicaffeoylquinic acids (48%) and luteolin-7-O-beta-D-glucuronide (3.4%) compared to cynarin (1,3-DCCA), the main choleretic compound of *Cynara scolymus* L. IPRL experiments revealed a dose-dependent increase in bile flow (23-44-47%) by the Achillea fraction. Choleresis was two- to three-fold higher than that of cynarin. The combined effect of DCCAs and luteolin-7-O-beta-D-glucuronide stimulated bile flow more effectively than the single compound cynarin. Due to their polar structure, these compounds are quantitatively extracted into teas and tinctures; hence, according to the authors, they seem to be the choleretic active principles in the traditional application forms of yarrow.

- Antimicrobal activity

A lipophilic extract of **aerial parts** of *Achillea millefolium* (hexane: ether: methanol=1:1:1 solvent, DER approx. 11:1) has been tested for antimicrobial activity in a disk diffusion assay against five bacteria (*Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Salmonella enteritidis*) and two fungi (*Aspergillus niger* and *Candida albicans*). The extract possessed a broad spectrum of antimicrobial activity against all tested strains (Stojanovic et al. 2005).

A 95%-ethanolic extract, from fresh plant *(Achillea millefolium*) exhibited antimicrobial activity against *Mycobacterium phlei,* but not against fungi or Gram-positive or Gram-negative bacteria (Dornberger and Lich 1982).

A 95% methanolic extract of powered **aerial parts of yarrow** *(Achillea millefolium* L.) inhibited 15 different strains of the Gram-negative bacterium *Helicobacter pylori* with MICs in the range of 1.56-100 microg/mL (Mahady et al. 2005).

The *in vitro* antimicrobial activities of the essential oil and of the methanol extracts of *Achillea millefolium* subsp. *millefolium* Afan. (Asteraceae) were investigated. The oil showed antimicrobial activity against *Streptococcus pneumoniae*, *Clostridium perfringens, Candida albicans, Mycobacterium smegmatis, Acinetobacter woffii* and *Candida krusei* while water-insoluble parts of the methanolic extracts exhibited slight or no activity (Candan et al. 2003).

- Haemostyptic activity

A 5% m/V hot water infusion of yarrow (*Achillea millefolium)* significantly shortened recalcification time (a test of blood coagulation) in human plasma to 43% of that of the reference substance, 0.9% sodium chloride ($p<0.001$). The flowering herb had the highest hamostypic activity, whereas pressed juice significantly prolonged blood coagulation ($p<0.05$ to $p<0.001$) (Sellerberg and Glasl 2000).

***In vivo* studies**

- Antiprotozoal activity

In this study, the efficacy of herbal extracts of Thymus vulgaris (thyme) and *Achillea millefolium* (yarrow), propolis hydroalcoholic extract and systemic glucantime against cutaneous leishmaniasis in Balb/c mice were evaluated. A total of 45 mice were randomised into five groups each including nine mice. They were treated with pure ethanol 70 degrees, systemic glucantime, *Achillea millefolium* hydroalcoholic extract, Thymus vulgaris hydroalcoholic extract and propolis hydroalcoholic extract for six weeks. The statistical tests including student t-test were used for analysis. Mean of ulcer size reduction were -17.66, -22.57, 43.29, 36.09 and 43.77% for the alcohol, glucantime, yarrow, thyme and propolis groups, respectively. The results were suggestive that Thymus vulgaris, *Achillea millefolium* and propolis hydroalcoholic extracts were significantly more effective in reduction of ulcer size as compared with glucantime ($p = 0.006$, 0.002 and 0.008, respectively) (Nilforoushzadeh et al. 2008).

- Analgesic effects

The aim of the study of Noureddini and Rasta was to assess the analgesic effects of aqueous extract (AE) of *Achillea millefolium* L. in the rat's formalin test. Oral administration of different doses of AE (80, 160 and 320 mg/kg) induced a dose-dependent antinociception, both in the first and second phases of the formalin test. The results of the present study support the proposal that *Achillea millefolium* L. has analgesic effects. These findings justify the traditional use of the plant for treating pain and suggest that its activity may result from its central action (Noureddini and Rasta 2008).

- Anti-inflammatory effect

An aqueous extract of the dry flower heads of *Achillea millefolium* has been found to possess anti-inflammatory activity as measured by the yeast–induced mouse paw oedema test. Fractionation has resulted in the isolation of a material which reduces inflammation by 35% compared to 44% and 26% respectively for the same doses (40 mg/kg body weight) of indometacin and phenylbutazone. The authors emphasised that the concentrate is water-soluble, nonsteroidal and has a very low toxicity. It was further reported, that physical and chemical studies showed the active fraction to be a mixture of protein-carbo-hydrate complexes (Goldberg et al. 1969).

A dry 80%-ethanolic extract from the aerial parts of yarrow (*Achillea millefolium* L.) administered orally at 100 mg/kg, inhibited oedema in the carrageenan-induced rat paw oedema test by 29% ($p<0.05$) compared to 45% by indometacin at 5 mg/kg. ($p<0.01$) (Mascolo et al. 1987)

- Gastro protective effects:

Seven days after induction of chronic gastric lesions in rats by acetic acid a hot (70ºC) water extract (yield 36%, approximately DER: 2.8:1) from the aerial part of yarrow (*Achillea millefolium* L.), was administered orally at 100 or 300 mg/kg/day for 7 days. Compared to controls, a significant and dose-dependent healing effect was observed ($p<0.05$, ED_{50} = 32.4 mg/kg). However, the same treatment started 1 day after injection of acetic acid did not prevent the formation of gastric ulcers. Oral pre-treatment of rats with the extract one hour before induction of acute gastric lesions by ethanol had a dose-dependent protective effect ($p<0.05$, ED_{50} = 936 mg/kg). Gastric lesions induced by indometacin one hour after subcutaneous administration of the extract were significantly reduced ($p<0.05$) only with the highest dose tested, 2000 mg/kg (Cavalcanti et al. 2006).

- Hepato-protective effect:

A dry extract of aerial parts of yarrow (5.5:1, 70% methanol) administered intra-peritoneally at 150, 300, and 600 mg/kg body weight exerted a protective effect against D-galactosamine+lipopolysaccharide-induced hepatitis in mice, significantly and dose-dependently reducing plasma ALT and AST levels in treated animals compared to controls ($p<0.05$). In liver histopathology an absence of congestion and focal necrosis was observed in treated animals, with dose-dependent improvement in cellular swelling and the number of apoptotic cells. Pre-treatment of the animals with the extract reduced mortality from 100% to 40% (Yaeesh S et al. 2006).

The antihepatotoxic activity of dry extracts of yarrow (*Achillea millefolium* L.), of varying polarity (following extraction with chloroform, methanol or water) was evaluated in rats treated with carbon tetrachloride or paracetamol as toxicants. Liver function was assessed by determining the levels of serum glutamic oxalacetate transaminase (ALAT) and serum glutamic pyruvic transaminase (ASAT), increases indicating necrosis of the liver. Intraperitoneal administration of the extract at 50 mg/kg reduced ALAT/ASAT levels by 50-96% in carbon tetrachloride-treated animals and 41-91% in paracetamol-treated animals ($p <0.05$) (considering the difference in levels between untreated and toxicant-treated animals as 100%) (Gadgoli and Mishra 1995).

- Cardiac activity

The effects of *Achillea millefolium* total extract on the electrocardiogram, cardiac enzymes and serum electrolytes in 12 clinically healthy sheep were investigated. The treatment group was administered intravenously a total extract of *Achillea millefolium* (no details on DER and extraction solvent are available) at a dose of 20 mg/kg. The control group received normal saline. Base-apex electrocardiogram was recorded up to 2 hours and blood samples for measuring an extensive array of serum enzymes and electrolytes were collected until 3 days after administration. Some occasional changes in electrophysiological parameters were observed, whereas *Achillea millefolium* had no significant effect on serum enzymes and electrolytes. The authors concluded that *Achillea millefolium* extract increased cardiac contractility after 2 hours (Rahchamani et al. 2008 - abstract).

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

No pharmacokinetic data are available.

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

- Single dose toxicity

Yarrow dry extracts of varying polarity (following extraction with chloroform, methanol or water) were non-toxic in mice; the intraperitoneal LD_{50} was determined as 1.5 g/kg body weight (Gadgoli and Mishra 1995).

Non-fasted rats of both sexes were treated with a single dose of hot water extract (yield 36%, approximately DER: 2.8:1) from the **aerial** part of yarrow (*Achillea millefolium* L.) at doses of 3 and 10g/kg orally or 1 and 3g/kg intraperitoneally. No toxic symptoms over the observational period of 14 days were observed (Cavalcanti et al. 2006).

After intraperitoneal treatment of mice with an extract (70% aqueous-methanol solution, yield 18%, approximately DER: 5.6:1) of the **aerial parts** of yarrow (*Achillea millefolium)* at 3g/kg body weight no changes in behaviour were apparent during a 6-hour observation period and no mortality was observed after 24 hours (Yaeesh et al. 2006).

According to a safety assessment of its use in cosmetics, the oral and subcutaneous LD_{50} values of yarrow, *Achillea millefolium* L. extract (2% **flowers** in propylene glycol and water) in mice were both 1g/kg (*Anonymous 2001*).

- Repeated dose toxicity

Female and male Wistar rats were treated daily with a hot water extract (yield 36%, approximately DER: 2.8:1) from the **aerial part** of yarrow (*Achillea millefolium* L.) in doses of 0.3-1.2 g/kg, p.o./day or vehicle (water, 10 ml/kg/day) for 28 or 90 consecutive days. Rats were observed throughout the study for morbidity, mortality and vital signs and in the end of the study, fairly extensive pathological, histopathological and biochemical investigations were carried out. Occasional deviations from controls or reference values were observed, but none of the changes observed after treatments with the extract correlated with dose or time of exposure in either female or male animals and did not exceed the reference range of variation (Cavalcanti et al. 2006).

- Genotoxity studies:

No adequate genotoxicity studies have been performed with Millefolii herba.

A herbal tea from *Achillea millefolium* provided some, albeit inconclusive evidence of genotoxicity in the wing Somatic Mutation and Recombination Test (SMART). Quercetin and rutin, two flavonols present in beverages of plant origin, exhibited weak genotoxic activity in somatic cells of *Drosophila*. The standard herbal teas (infusions) were prepared by adding 20 g dry tea to 100 ml boiling tap water and allowing it to draw for 10 min (Graf et al. 1994).

The genotoxicity evaluation of the essential oil of *Achillea millefolium* was performed at concentrations of 0.13 microL/mL, 0.19 microL/mL and 0.25 microL/mL with a heterozygous diploid strain of *Aspergillus nidulans*, named A757//UT448, with green conidia. A statistically significant increase of mitotic recombinants due to either the induction of mitotic non-disjunction or crossing-over was reported after oil treatment with 0.19 microL/mL and 0.25 microL/mL concentrations (de Sant'anna et al. 2009 - abstract).

In the present study, the action of an infusion prepared from the **leaves** of *Achillea millefolium* L. (Am) was assessed *in vitro* on chromosomal aberration formation in a human lymphocyte system alone or in combination with the alkylating agent mitomycin C (MMC) and the DNA repair inhibitor cytosine-beta-arabino-furanoside (Ara-C). The cells were cultivated for 72 hours and treated continuously with the Am infusion at dosages of $3.5 \times 10^{(-4)}$ g/ml culture medium. Treatments with MMC (0.30 microg/ml) or Ara-C ($5 \times 10^{(-7)}$ microg/ml) were administered after 48 hours of cell culture. Each sample (five individual) was exposed to six treatments (control with PBS; Am; MMC; MMC+Am; Ara-C; and Ara-C+Am) and 100 cells were analysed per cell culture. The used dose of the infusion did not cause clastogenic effects significantly different from the negative control (control=1%; Am=1.8%). Nevertheless, the aberrant cell frequency after MMC treatment significantly increased by the Am infusion (MMC=32.4%; MMC+Am=44%), especially when the chromatid break types number was scored (MMC=151; MMC+Am=249). Regarding DNA repair inhibition by Ara-C, the Am infusion did not cause a significant reduction in aberrant cell frequency (Ara-C=15.8%; Ara-C+Am=14.4%). These results indicate that the plant infusion *per se* does not possess clastogenic activity, but can influence the clastogenic action of MMC and Ara-C on DNA break induction, *in vitro* (Roncada et al. 2004).

- Reproductive toxicity

Because yarrow has traditionally been used as an abortifacient, emmenagogue, contraceptive, and for stimulating uterine contractions, it is contra-indicated for use in pregnancy. Two experimental animal studies have addressed reproductive toxicity of yarrow. In a study of Boswell-Ruys et al. (2003), female rats were administered orally, by gavage, 2.8 g/kg body weight/day (56 times the human dose)

of ethanolic solution of a commercial yarrow leaf extract on either gestation days (GD) 1-8 or GD 8-15. Two groups of controls were included; the first received water and the second received an equivalent dose of ethanol to that found in the yarrow preparation over the two gestation periods. On GD 20, rats were sacrificed, placentae were weighed, and corpora lutea counted. The foetuses were weighed and examined for signs of external, internal or skeletal malformations. The dose used was not materno-toxic. There was no increase in pre- or post-implantation losses. Placental weights were increased in rats treated with yarrow on GD 8-15 compared to water and ethanol controls and on GD 1-8 compared to water control foetuses. Body weight was reduced in foetuses exposed to yarrow on GD 8-15 compared to water control foetuses. There was no difference in incidence of external or internal malformations. In conclusion, a 2.8 g/kg body weight daily dose of yarrow was associated with reduced foetal weight and increased placental weight (Boswell-Ruys et al. 2003).

Another study (Dalsenter et al. 2004) evaluated the toxicity of the exposure to the aqueous extract from **leaves** of *Achillea millefolium* L. on reproductive endpoints in Wistar rats. Adult male rats were treated daily with yarrow extract (0.3, 0.6 and 1.2 g/kg/day) during 90 days by oral gavage. Endpoints including reproductive organ weights, sperm and spermatid numbers as well as sperm morphology were evaluated. No clinical signs of toxicity were detected over the treatment period, and body weight gain was similar in all groups. A significant increase in the percentage of abnormal sperm in the group treated with the highest dose of yarrow extract was detected with no other important changes in the other reproductive endpoints studied in the male rats. Furthermore, a 3-day treatment of immature female rats did not show any uterotrophic effects (Dalsenter et al. 2004).

The effect of hydro-alcoholic extract (200, 400, 800 mg/kg) of *Achillea millefolium* L. yarrow **flowers** on spermatogenesis of 50 Wistar rats was investigated by intraperitoneal administration. The animals were divided into 3 experimental groups (10 rats in each group) and a control group (10 rats received distilled water) and 1 sham group (10 rats received nothing). At the dose of 200 mg/kg, there was no effect on spermatogenesis and all cells had normal arrangement and count. At the dose of 400 mg/kg, a significant difference in cell arrangement and cell count was observed, but after 22 days, on which 5 rats of this group were kept without any extract administration, there was no significant difference between them and the control group, so at this dose the effect was reversible. At the dose of 800 mg/kg a significant effect was observed as well, but after 22 days it was not reversible (Takzaree et al. 2008).

- Sensitisation potential

Sensitisation potential was assessed in groups of guinea pigs (Hausen et al. 1991) in a modified Freund's complete adjuvant method, by 0.1% and 1% crude ethylether extract of the whole yarrow plant, and by 0.1% and 1% crude ethylether extract of the flowers. The sensitisation potential of the sesquiterpene lactone alpha-peroxyachifolid was also tested at 0.01% and 0.1% using groups of 10 guinea pigs and at 1% using a group of 3 guinea pigs. All animals tested with extracts of the whole plant and with flower extract were sensitised. Sesquiterpene lactone alpha-peroxyachifolid was identified as a strong sensitiser. Other known yarrow constituents like dehydromatricaria ester and pontica epoxide appear to play no role.

3.4. Overall conclusions on non-clinical data

The above mentioned pharmacological studies made the proposed indications plausible.

The indication of temporary loss of appetite is based on the bitter component(s) of the herbal substance. A limit for the bitter value of up to 5000 is included in the German Pharmacopoeia 1997.

The beneficial effect on mild, spasmodic gastro-intestinal complaints including bloating, and flatulence can be supported by the experiments on the inflammatory, antispasmodic and choleretic activity of the

herbal substance. These activities are connected to the sesquiterpenes, phenolic (such as dicaffeoylquinic acids) and flavonoid content of yarrow.

The antispasmodic and analgesic properties of the plant may support its effectiveness in the indication of symptomatic treatment of minor spasms associated with menstrual periods.

The studies on antimicrobial and antiphlogistic activity may make the wound healing effect plausible.

Adequate tests on reproductive toxicity genotoxicity and carcinogenicity have not been performed. Three experimental studies on embryotoxicity and reproductive toxicity demonstrate relatively marginal effects. Guinea pig sensitisation tests indicated some sensitisation potential for yarrow extracts and one sesquiterpene lactone component.

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

No data.

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

No data.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data.

4.2.2. Clinical studies (case studies and clinical trials)

There was no clinical study performed with yarrow herb as a single component.

Only studies with combination products can be found.

The aim of a randomised, placebo controlled trial was to test the efficacy of a hydro-ethanolic extract of tri-herbal combination (Eleutherococcus, *Achillea millefolium* and Lamium album) on atopic dermatitis in 49 patients treated for 2 weeks. Patients were followed until week 8. Forty-four patients completed the study. Twenty–two patients were treated with the study medication and 22 with placebo. The study medication was well tolerated without significant side effects.

The response to the study medication was significant in objective and subjective parameters. Patients maintained partial remission until the end of follow-up. The placebo-treated group had a similar response without a significant difference. In conclusion it was found that the treatment with the tri-herbal combination for atopic dermatitis does not differ from treatment with placebo (Shapira et al. 2005).

A herbal preparation containing 110 mg feverfew *(Chrysanthemum parthenium)*, 90 mg American aspen *(Populus tremuloides)* and 60 mg milfoil (*A. millefolium*,yarrow) was tested for its efficacy in the treatment of mild to moderate osteoarthritis. Thirty-five patients who were taking NSAIDs underwent a

2-week washout phase before being randomised to receive the herbal preparation (three tablets daily) or ibuprofen (400 mg three times daily) administered for 2x21 days in a double-blind, crossover randomised controlled trial with the double-dummy technique. Patients were allowed to take dextropropoxyphene as a rescue medication for pain relief. The number of tablets taken was recorded and used to assess the change in condition. The primary outcome measures of pain (when resting and working) and walking ability were assessed using a symptom score on a scale of 1–4 (none, mild, moderate, strong). A non-significant trend of symptom reduction was observed in both groups, with no significant difference between groups. Gastrointestinal complaints were more frequent in patients treated with ibuprofen (Long et al. 2001).

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

No data.

4.3. Overall conclusions on clinical pharmacology and efficacy

As there are no clinical studies thus well-established indication can not be suggested.

Taking into consideration the long-standing use of the comminuted herbal substance, the liquid extract, the tincture and the expressed juice from fresh herb, the traditional use in the proposed indications is plausible.

5. Clinical Safety/Pharmacovigilance

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

Irritation

Yarrow, *Achillea millefolium* L., is one of the most common species of the Compositae family. Cases of allergic contact dermatitis have been described since 1899. Although 10 sesquiterpene lactones (SL) and 3 polyines have previously been identified, the responsible allergens in yarrow have not been established. A reinvestigation of short ether extracts of yarrow revealed the presence of five unsaturated hitherto unknown guaianolides of peroxide character. The main SL, identified as a strong sensitiser in guinea pig sensitisation experiments, was named alpha-peroxyachifolid. The minor SL also contribute marginally to the sensitising capacity, while other known yarrow constituents like dehydromatricaria ester and pontica epoxide appear to play no role. A 5-year follow-up (1985-1990) of Compositae-sensitive patients showed that more than 50% reacted when tested with a short ether extract of yarrow. Exacerbation of the patch test sites by irradiation with UV light was never observed (Hausen et al. 1991).

A Compositae plant mixture consisting of short ether extracts of arnica, German chamomile, feverfew, tansy, and yarrow has been included in the standard series for several years (1985 to 1990) to study the frequency of allergic reactions to Compositae (Asteraceae) species. One hundred and eighteen out of 3,851 tested individuals gave a positive response (3.1%). Further tests with the single species of the mixture and some additionally tested extracts of chrysanthemums and laurel oil (bay leaf; Lauraceae) revealed a high percentage of reactions to feverfew (70.1%) and lower responses to chrysanthemums (63.6%), tansy (60.8%), chamomile (56.5%), arnica (51.8%), yarrow (51.8%), and the cross-reacting laurel oil (50.5%). Ten out of 85 reacted to arnica alone. The results show that it is important to test Compositae extracts in patients with allergic contact dermatitis because these contain (in contrast to a mixture of pure sesquiterpene lactones) other constituents (e.g., polyacetylenes, thiophenes) that may also contribute to the acquired hypersensitivity. Unrevealed sources of hand and

face eczema (including airborne contact dermatitis) might be diagnosed more frequently (Hausen 1996 - abstract).

5.2. Patient exposure

No data.

5.3. Adverse events and serious adverse events and deaths

None known (German Commission Monograph 1990, Blumenthal et al. 1998, 2000).

In case of allergies to Asteraceae, itching and inflammatory changes in the skin with formation of vesicles (yarrow dermatitis) may occur, in which case the treatment must be stopped immediately (Bisset NG. 1994).

Rarely allergic reactions with rash, formation of vesicles and pruritus can occur after internal or external use. Cases of contact dermatitis ("meadow dermatitis") and cross reaction with other Compositae can occur (Hänsel et al. 1992).

Allergic reactions to yarrow (e.g. dermatitis) have been documented, and positive patch tests have been produced in individuals sensitised to other plants. An instance of yarrow tea causing a generalised eruption in a sensitised individual was reported in 1929 (Barnes et al. 2007).

Several cases of contact allergy have been reported (ESCOP Supplement 2009).

Numerous reports of allergic contact dermatitis have been published. Direct contact with the crude drug or its preparations may cause hypersensitivity reactions of the skin or mucosa, such as rash, formation of vesicles and pruritus in sensitive individuals (WHO 2009).

Compositae dermatitis occurred in a 9-year-old boy with a strong personal and family history of atopy. Positive patch test reactions were 2+ for yarrow (*Achillea millifolium*), the eruption resembled atopic dermatitis morphologically but was prominent on the palms and face and dramatically spared the area of the boy's feet covered by his shoes. The condition has always been seasonal, worsening in summer, especially July, and it clears on avoidance of contact. This case is believed to represent a contact dermatitis to oleoresins of Compositae plants; inhalants as a cause of systemic aggravation are not likely to be important in this patient (Guin 1987 - abstract).

Five months after her first contact with dried flowers of yarrow a 44-year-old woman began to experience rhinitis, asthma and urticaria symptoms in the workplace when she handled these dried flowers as an instructor of personnel making dried flower arrangements (centrepieces and baskets). She had a clinical history of spring seasonal rhino-conjunctivitis and asthma but no family history of atopy. The physical examination was normal. Basal spirometry and chest X-ray was normal. Methacholine inhalation test was positive with a PC20 of 2.5 mg/ml. Total serum IgE was 7.94 kU/l. Skin prick test with aqueous extracts from dried flowers were positive to yarrow (10x7 mm). Specific Inhalation Bronchial Challenge with aqueous extract of yarrow (1.25 mg/ml) elicited an asthmatic response with a fall in FEV1 of 31%. Specific IgE (EAST) with yarrow flowers was 0, 9 kU/l respectively. Immunoblotting with yarrow flowers revealed several IgE binding bands of 51, 21 and 18 kDa. Occupational respiratory symptoms caused by decorative flowers are seldom reported in the literature (Compes et al. 2006).

In a clinical testing with 20 subjects, product formulations containing 2% of extracts of the crude drug in propylene glycol and water were generally not irritating. In provocative testing, patients reacted to a Compositae mixture that contained the crude drug, as well as to the crude drug alone. In clinical testing, a formulation containing 0.1% yarrow extract (propylene glycol and water) was not a

sensitiser in a maximization test and alcoholic extracts of aerial parts of *A. millefolium* did not produce a phototoxic response (Anonymous 2001).

Proposed wording in the monograph:

Hypersensitivity reactions of the skin have been reported. The frequency is not known.

5.4. Laboratory findings

No data are available.

5.5. Safety in special populations and situations

Contra indications (hypersensitivity and allergic potential to be both covered)

Allergy to yarrow and other Compositaes (Blumenthal et al. 1998, 2000, Bradley 1992, Hänsel et al. 1992, Newal et al. 1996).

Warnings and precautions for use

The use in children under 12 years of age is not recommended due to lack of adequate data.

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indication 4)

If signs of skin infection are observed, a doctor or a qualified health care practitioner should be consulted.

For tinctures, extracts containing ethanol the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

Drug interactions

None documented. However, the potential for preparations of yarrow to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered. There is limited evidence from preclinical studies that achilleine, a constituent of yarrow, has anticoagulant activity, although the clinical relevance of this, if any, is not clear (Barnes et al. 2007).

Assessor's comment: Because the above mentioned drug-interactions are only assumptions, interactions appear as "None reported" in the monograph

Use in pregnancy and lactation

Yarrow should not be taken during pregnancy. It is reputed to be an abortifacient and to affect the menstrual cycle, and the volatile oil contains trace amounts (0.3%) of the abortifacient principle thujone. Excessive use should be avoided during lactation (Newal et al. 1996, 2007).

Assessor's comment: Not taken into consideration because preparations of yarrow contain only trace amount of thujone. The herb contains 0.3-1.4% volatile oils according to Blumenthal et al. 2000, which may contain 0.3% thujone, see above. The daily dose is 2-4 g three times daily which means 6-12 g/day of the herbal substance with a 0.27-0.5 mg content of thujone/day. This concentration is considered too low to present a risk to human heath (see Public statement on the use of herbal medicinal products containing thujone EMA/HMPC/732886/2010*).*

The standard sentences are suggested in the monograph:

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

Overdose

No case of overdose has been reported.

Drug abuse

None reported.

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

No studies on the effect on the ability to drive and use machines have been performed.

5.6. Overall conclusions on clinical safety

The medicinal use of yarrow preparation can be considered safe. Only the reported hypersensitivity reactions may present a risk therefore for safe use the sentence of "Hypersensitivity to the active substance and to other plants of the *Asteraceae* (*Compositae*) family" was included in the Contraindication section of the Community monograph.

The known toxic principle thujone has been documented as a minor component of yarrow oil, but the concentrations are too low to present a risk to human health.

Dry methanolic and 10%-methanolic extracts of the aerial parts of *A. millefolium* showed oestrogenic activity in an *in vitro assay*, based on recombinant MCF-7 cells (Innocenti et al. 2007), but in two experimental animal studies there were no increases in pre- or post-implantation losses (Boswell-Ruys et al. 2003).

Since there are insufficient data, the use during pregnancy and lactation is not recommended.

6. Overall conclusions

Yarrow herb has been in medicinal use for a period of at least 30 years as requested by Directive 2004/24/EC, thus the requirement for the qualification as a traditional herbal medicinal product is fulfilled (long-standing use dating back to ancient time).

The pharmacological studies on the anti-inflammatory, spasmolytic, choleretic, antimicrobial effects of yarrow may contribute to the proposed traditional indications. These properties can be associated with the sesquiterpenes, phenolic (such as dicaffeoylquinic acids) and flavonoid content of the herbal substance.

The benefit-risk balance can be considered positive. The only possible risk, the hypersensitivity reaction, is taken into consideration and the patients' attention is drawn to it properly.

As there are insufficient data, the use during pregnancy and lactation is not recommended.

Due to inadequate data on genotoxicity the inclusion of Millefolii herba in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

Annex

List of references