15 September 2010
EMA/HMPC/290309/2009
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Achillea millefolium* L., herba

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

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

Draft

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

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Achillea millefolium* L., herba. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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Table of contents

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 6th ed. (2008) Yarrow

Extra Pharmacopoeia Martindale XXV. Edition (Todd RG 1976)

Herbal Medicines (Newal CA et al. 1996), (Barnes J at al. 2007)

WHO Monographs (Volume 4, 2009)

ESCOP Monographs (Supplement 2009)

- Fresh or dried aerial (aboveground) part collected during the flowering season of *Achillea millefolium*

This definition can be found in:

Pharmacopoea Hungarica Editio VI. Tomus III, 1967

Hagers Handbuch der Pharmazeutischen Praxis 1969 (Kern W.)

German Comission E Monograph 1990

British Herbal Pharmacopoeia 1996 (dried aerial parts)

British Herbal Compendium Volume 1, 1992 (dried aerial parts)

WHO Monographs (Volume 4, 2009)

ESCOP Monographs (Supplement 2009)

Assessor's comment: MLWP decided to use the definition of European Pharmacopoeia 6th ed. (2008) Yarrow on it March meeting 2010.

- Herbal preparation(s)

Communited herbal substance as infusion for tea preparation (Augustin B 1948, Todd RG 1967, BHP 1974, Rácz G et al. 1984, German Commission E monograph 1990, Blumenthal M et al. 1990, Wren RC 1988, Bisset NG 1994, Newal CA et al. 1996, Hänsel R et al. 1992, Bradley R 1992)

Expressed juice (1:1) from fresh herb (Blumenthal M et al. 1990, Hänsel R et al. 1992)

Liquid extract (1:1), extraction solvent: ethanol 25% (V/V) (Wren RC 1988, Bradley R 1992, Newal CA et al. 1996, BHP 1974)

Tincture (1:5), extraction solvent: ethanol 45% (V/V) (Bradley R 1992, Newal CA 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 lost of appetite.

1.1.1. 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 to 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 M 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 quantity in the different plant materials.

Benedek B et al. (2007 a) developed a SPE-HPLC/UV method that allows quantification of the phenolic constituents in the different taxa in oder 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 B 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:	+ 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 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**
Millefolii herba (names of the products: řebříčkový čaj, řebříčková nať) (CZ)	oral use: for symptomatic treatment of mild gastro-intes-tinal complaints, at loss of appetite oromucosal use: for symp-tomatic 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 tea spoon)/250 ml of boiling water/15 minutes 2 – 3 times dailyfor oromucosal and topical use: 3 to 4.5 g (2 – 3 tea spoons)/ 250 ml of boiling water/15 minutes	1997
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 x daily 4.3 ml (= 4.2 g) liquid containing 100% tincture	At least since 1976 WEU
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 x daily 5 ml liquid containing 100% expressed juice	At least since 1976 WEU
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 x daily 10 ml liquid containing 100% expressed juice	At least since 1990 (already authorized in the former GDRWEU
20 g extract from Millefolii herba (1:5) 80 g ethanol (29 V/V%) oral solution; (HU)	Treatment of inflammatory disorders of stomach and 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)	Digestivum, spasmoliticum, appetizer	3x3-4 coated tablets (corresponding to 3x 570-760 mg herbal substance)	Since 1996 Healing products
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 in 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 R et al. 1992), Expanded Commission E Monograph (Blumenthal 2000).

- Articles and references retrieved from data bases (Pubmed, Toxnet) or internet sources (e.g. Google) until the end of 2009. The term of *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 Blumental M et al. (2000) yarrow has been used as medicine by many cultures for hundreds of years (Budavari S 1996, Zeylstra H 1997). Its English common name is a corruption of the Anglo-Saxon name *gearwe*; the Dutch, *yerw*. The genus name *Achillea* may have been derived from the Achilles of Greek mythology, which was fabled to have had his wounds treated by topical use of the herb. The species name *millefolium* is derived 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 United States Pharmacopoeia. Additionally, it is listed in the Indian Ayurvedic Pharmacopoeia for fevers and wound healing (Karnick CR 1994).

<u>European National pharmacopoeial monographs:</u>

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 (DAB 10) (mentioned by Bisset NG 1994)

Austrian, Czech, French, Romanian Pharmarmacopoeias (mentioned by Newal CA et al. 1996)

<u>Other monographs:</u>

Hungarian Herbal Drugs (Augustin B et al. 1948)

German Commission E monograph (1990)

Hagers Handbuch (Kern W et al. 1969, Hänsel R et al. 1992)

Potter's New Cyclopedia of Botanical Drugs and Preparations (Wren RC 1988)

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

Evidence regarding the indication/traditional use

In Belgium (cited in Bradley PR 1992):
Circulaire No. 367 of July 1991: Traditionally used topically as soothing antipruriginous application for dermatological affection.

In France (cited in Bradley PR 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, adstringents, choleretic, in problems of menstruation, bleeding for haemorrhoids, varicose vein, as diuretic by hypertension, diaphoretic, liver trouble, emmenagogue, abortifacient, pertusis, lung tuberculosis, haematoma, as in infusum (15-20:200), expressed juice from fresh herb for spring-cure. Externally it used for healing wounds and ulcers similarly as chamomile (Kern W et al. Hagers Handbuch 1969).

Internally: loss of appetite; dyspeptic complaints such as mild, spasmodic disturbances in the gastrointestinal region. In hip baths: painful, cramp-like condition of psychosomatic origin (in the lower part of female pelvis) (German Commission E monograph 1990, Hänsel R 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. in bleeding from haemorrhoids, and in problems of menstruation and to remove perspiration (baths) (Bisset NG Herbal drugs and Phytopharmaceuticals 1994, Hänsel R et al. 1992).

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

In Romania (Rácz G et al. 1984):
It is used in the inflammation of the mucous membrane of the stomach, gastric-, duodenal ulcer, catarrh of the colon. It is used externally for bathing of baby, of patients with eczema and as rinse in paronditis.

In UK:
Diaphoretic, stimulant, and haemostatic (Todd G Extra Pharmacopoeia Martindale 1967)

Indications: feverish conditions, common cold; digestive complaints. Other uses: loss of appetite, hypertension, menstrual irregularities. It used topically for slow-healing wounds and skin inflammation. (Newal CA Herbal Medicines 1992, Bradley PR British Herbal Compendium 1992, British Herbal Pharmacopoeia 1983, 1990, Wren RC Potter's New Cyclopedeia of botanical drugs and Preparations 1988, First published in 1907).

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

The proposed indications for the monograph:

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

1) Traditional herbal medicinal product used in temporary loss of appetite.

2) Traditional herbal medicinal product for symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.

4) Traditional herbal medicinal product for treatment of small superficial wound.

Indications based on literature:

3) For symptomatic treatment of minor spasm associated with menstrual periods.

Evidence regarding specified substances/preparations

Herbal substance

Not applicable.

Herbal preparations

In the literature

Communited herbal substance as infusion for tea preparation (Kern W et al. 1969, Hansel R et al. 1992, BHP 1974, 1983, Augustin B et al. 1948, Rácz G et al. 1984, German Commission E monograph 1990, Wren RC 1988, Bisset NG 1994, Newal CA et al. 1996, Bradley R 1992, Bisset NG 1994, Newal CA et al. 1996)

Liquid extract (1:1), extraction solvent: ethanol 25% (V/V) (BHP 1974, Wren RC 1988, Bradley R 1992, Newal CA et al. 1996)

Tincture (1:5), extraction solvent: ethanol 45% (V/V) (BHP 1974, Bradley R 1992, Newal CA et al. 1996)

Products on the market for more than thirty years

Communited herbal substance
Expressed juice (1:0.65-0.85) from fresh herb
Expressed juice (1:0.84-0.93) from fresh herb

Assessor's comment: These two expressed juice were drawn together in one preparation according to the suggestion of Subgroup discussion in May 2010:

Expressed juice (DER 1:0.6-0.9) from fresh herb
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 31.5% (V/V)

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 RG 1967, Bradley PR 1992, Hänsel R et al. 1992)
Daily dose: 4.5 g of yarrow herb (German Commission E monograph 1990, Bisset NG 1994)

Wording of the package insert, from the German Standard Licence:
Hot water (ca. 150 ml) are 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 drunk warm three or four times a day between meals (in Bisset NG 1994, Hänsel R et al. 1992).

Single dose: 1.5 g (Kern W 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 more than 30 years in Poland).

Expressed juice from fresh herb:

- DER: 1:0.6-0.9; 3 x daily 5 ml liquid containing 100% expressed juice (product on the market more than 30 years)
- DER: 1:0.8–1.0; 2 x daily 10 ml liquid containing 100% expressed juice (product on the market more than 30 years)

Assessor's comment: These two expressed juice were drawn together in one preparation according to the suggestion of Subgroup discussion in May 2010:

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

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

Tincture (1:5), extraction solvent: ethanol 45% (V/V): 2-4 ml three times daily (Bradley R 1992, Newal CA et al. 1996, BHP 1974)

Tincture (1:5), extraction solvent: ethanol 31.5% (V/V) 4 x daily 4.3 ml (= 4.2 g) (products on the market more than 30 years)

Indication 3)

1 spoon comminuted herbal substance per cup, as infusion several times a day (the Madaus handbook 1938, Fintelmann 2002 Lehrbuch der Phytotherapie)

Indication 4)

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

The proposed posology for the monograph

Oral use

i) Herbal substance

Not applicable

ii) Herbal preparations

Indication 1) and 2)

a) 2-4 g comminuted herbal substance as infusion three or four times a day between meals

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

c) Liquid extract (1:1), extraction solvent: ethanol 25% (V/V): 2-4 ml three times daily

d) Tincture (1:5), extraction solvent: ethanol 45% (V/V)

e) Tincture (1:5), extraction solvent: ethanol 31.5% (V/V) 4 x daily 4.3 ml (= 4.2 g)

Indication 3)

1-2 g comminuted herbal substance per cup, as infusion 2-3 times daily

Cutaneous use

Indication 4)

3.5 g of comminuted herbal substance as infusion applied as cold compresses 2-3 times daily

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 H 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 microg/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 partly mediated by inhibition of HNE and MMP-2 and -9 (Benedek B et al. 2007).

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 P et al. 2003).

- **Anti-oxidant effects**

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) scavaging 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 tested as well, and the antioxidant effects were correlated with the total amount of phenolic compounds contained in the extracts (Trouillas P 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 dismutate and glutation peroxidase activities, as well as by reduced glutathione content of the cells and decrease in lipid peroxidation (Konyalioglu S and Karamrenderes C 2005).

Steam-distilled and non-stilled plant material from yarrow *(A. millefolium* L.*)* was extracted with solvents of different polarity and resulting fractions were evaluated for their radical scavenging activity by the DPPH, NBT/hypoxanthine superoxide, and •OH/luminol chemiluminescence methods and for their antioxidant activity by the β-carotene blenching test. The total phenolic content was also determined by the Folin-Ciocalteu method. Both 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 I 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 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 F et al. 2003).

- **Anti-proliferative activity**

The above mentioned water-soluble fraction from a hydro-alcoholic extract of *Achillea millefolium* showed 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 P 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 down regulate 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 over expressing cells are not resistant to casticin, and its cell killing effect is observed even in p53 mutant or null cell lines (Haidara K 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 B et al. 2008).

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 L-T et al. 2002).

- **Estrogenic activity**

Dry methanolic and 10%-methanolic extracts of the aerial parts of *A. millefolium* showed oestregenic activity in transgenic MCF-7 cells. The lowest effective concentrations were 8.57 x 10^{-5} mg/ml and 2.8 x 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 x 10^{-4} mg/ml) luteolin (8.9 x 10^{-3} mg/ml) and their 7-O–glucosides (3.9 x10^{-5} mg/ml and 3.4 x10^{-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 endogen hormone. Both receptors, alpha and beta, can be activated by apigenin. Luteolin seems to have a very slight effect on beta and does not seem to activate alpha at all. However the role of apigenin in emmenagogic effects of *A. millefolium* – as traditionally reported- can not be defined on this basis (Innocenti G 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 L 1962).

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 flavonoidsis 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 S et al. 2006).

- **Choleretic effect**

In their work Benedek B et al. (2006) investigated a fraction from a 20% methanolic extract of the **arial part of yarrow** enriched in dicaffeoylquinic acids (48%) and luteolin-7-O-beta-D-glucuronide (3.4%) on its choleretic effect in the isolated perfused rat liver (IPRL) compared to cynarin (1,3-DCCA), the main choleretic compound of *Cynara scolymus* L. IPRL experiments revealed a dose-dependant 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.

- **Antimicrobial 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*). Extract possessed a broad spectrum of antimicrobial activity against all tested strains (Stonajovic G et al. 2005).

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

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

The *in vitro* antimicrobial activities of the essential oil and 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 F et al. 2003).

- **Haemostyptic activity**

A 5% m/V hot water infusium 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 U and Glasl H 2000).

In vivo studies

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 we 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 MA et al. 2008).

- **Analgesic effects**

The aim of the study of Noureddini M et al. 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 be resulted from its central action (Noureddini M, Rasta V 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. Fractination has resulted in the isolation of a material which reduces inflammation by 35% compared to 44% and 26% respectively fot the same doses (40 mg/kg body weight) of indomethacin and phenylbutazone. This concentrate is water-soluble, nonsteroidal and has a very low order of toxicity. Physical and chemical studies show this active fraction to be mixture of protein-carbo-hydrate complexes (Goldberg AS 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 N 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 formulation 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 the highest dose tested, 2000 mg/kg (Cavalcanti AM 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 C et al. 1995).

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

There are no pharmacokinetic data 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 C et al. 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 10 g/kg perorally or 1 and 3 g/kg intraperitoneally. No toxic symptoms over the observational period of 14 days were observed (Cavalcanti AM et al. 2006).

After intraperitoneal treatment of mice with an extract (70% aqueous-methanol solution, yield 18%, approximately DER: 5.6:1) of the **arial 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 after 24 hours (Yaeesh S et al. 2006).

According to a safety assessment for its use in cosmetics, the oral and subcutaneous LD_{50} values in mice of yarrow, *Achillea millefolium.* L. extract (2% **flowers** in propylene glycol and water) were both 1 g/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 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 morbility, 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 were correlated with dose or time of exposure in neither female nor male animals and did not exceed the reference range of variation (Cavalcanti AM et al. 2006).

- Genotoxity studies

No adequate genotoxicity studies have been performed with Millefolii herba.

An 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 JR et al. 2009).

In the present study the action **leaves** of *Achillea millefolium* L. (Am) infusion on chromosomal aberration formation in human lymphocyte system in vitro was assessed, associating it with the alkylating agent mitomycin C (MMC) and the DNA repair inhibitor cytosine-beta-arabin-furanoside (Ara-C). The cells were cultivated for 72 h and treated continuously with the Am infusion at dosages 3.5 x 10(-4) g/ml culture medium. Treatments with MMC (0.30 microg/ml) or Ara-C (5 x 10(-7) microg/ml) were administered after 48 h of cell culture. Each samples (five individual) were exposed to six treatments (control with PBS; Am; MMC; MMC+Am; Ara-C; and Ara-C+Am) and 100 cells were analyzed per cell culture. The used dose of the infusion did not cause clastogenic effects significantly different to the negative control (control=1%; Am=1.8%). Nevertheless, the aberrant cell frequency after MMC treatment was 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 do not has clastogenic activity, but can influence the clastogenic action of MMC and Ara-C on DNA break induction, *in vitro* (Roncada T 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 dosed, orally by gavage using 2.8 g/kg b.w./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 b.w. daily dose of yarrow was associated with reduced fetal weight and increased placental weight (Boswell-Ruys CL 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 PR 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 by intraperitoneal administration. The animals were divided into 3 experimental groups (10 rats in each group) and control group (10 rat 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 of cells had normal arrangement and account. At dose of 400 mg/kg, a significant difference in cell arrangement and cell count, but after 22 days, on which 5 number of this group was kept without any extract administration, there was no significant difference between them

and control group, so this dose was reversible. At dose of 800 mg/kg a significant effect was observed as well, but after 22 days it was not reversible (Takzaree N et al. 2008).

- Sensitization potential

Sensitization 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 extract of the whole yarrow plant, and by 0.1% and 1% crude extract of the flowers. The sensitization 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 sensitized. Sesquiterpene lactone alpha-peroxyachifolid was identified as a strong sensitizer. Other known yarrow constituents like dehydromatricaria ester and pontica epoxide appear to play no role.

- Cardiac activity

The effects of *Achillea millefolium* total extract on electrocardiogram, cardiac enzymes and serum electrolytes in 12 clinically healthy sheep were investigated. The treatment group were administered intravenously a total extract of *Achillea millefolium* at a dose 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 R et al. 2008).

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. According to German Pharmacopoeia (1997) the herbal substance must have a bitter value of maximum 5000.
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 spasm 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 sensitization tests indicated some sensitization 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 available.

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

No data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

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 randomized, placebo controlled trial was to test the efficacy of tri-herbal combination (Eleutherococcus, Achillea millefolium and Lamium album) on atopic dermatitis in. Forty-nine patients were included for 2 weeks of treatment. 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 tri-herbal combination for atopic dermatitis does not differ from treatment with placebo (Shapira MY 2005).

Gitadyl is an herbal preparation containing 110 mg feverfew *(Chrysanthemum parthenium)*, 90 mg American aspen *(Populus tremuloides)* and 60 mg milfoil (*A. millefolium*, yarrow). Thirty-five patients who were taking NSAIDs for mild to moderate ostearthrosis underwent a 2-week washout phase before being randomized to receive Gitadyl (three tablets daily) or ibuprofen (400 mg three times daily) administered for 2 x 21 days in a double-blind, crossover randomized 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 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 L et al. 2001).

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

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

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

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 commonest weeds 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 sensitizers of yarrow have not been detected. A reinvestigation of ether extracts of yarrow revealed the presence of 5 unsaturated hitherto unknown guaianolides of peroxide character. The main SL, identified as a strong sensitizer in guinea pig sensitization experiments, was named alpha-peroxyachifolid. The minor SL also contribute marginally to the sensitizing 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 an ether extract of yarrow. Exacerbation of the patch test sites by irradiation with UV light was never observed (Hausen BM et al. 1991).

A *Compositae* plant mixture consisting of 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 eighteen 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 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 BM 1996).

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

None known (German Comission Momograph 1990, Blumenthal M et al. 1998, 2000).

With 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 R 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 J 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+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 JD 1987).

Since 5 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 (10-7 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 E et al. 2006).

In a clinical testing with 20 subjects, product formulations containing 2% of extracts of the crude drug were generally not irritating. I provocative testing, patients reacted to *Compositae* mix 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 sensitizer 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 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 M 1998, 2000, Breadly R 1992, Hänsel R et al. 1992, Newal CA et al. 1996).

Warnings and precautions for use

The use in children and adolescents under 18 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.

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 J et al. 2007).

Assessor's comment: "None reported" is written in the monograph as the above mentioned drug-interactions are only assumptions.

Use in pregnancy and lactation

It is frequently considered that 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 CA et al. 1996, 2007).

Assessor's comment: Due to lack of adequate data a specific warning is not included in the monograph. Preparations of yarrow contain only trace amounts of thujone. The herb contains 0.3-1.4% volatile oil according to Blumenthal M 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 probably too low to present a risk to human health. 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 but the contra-indication paragraph of the monograph will draw the attention to it.

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 heath.

Dry methanolic and 10%-methanolic extracts of the aerial parts of *A. millefolium* showed estrogenic activity in an in vitro assay, based on recombinant MCF-7 cells, (Innocenti G et al. 2007), but in two experimental animal studies there was no increase in pre- or post-implantation losses (Boswell-Ruys CL 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 the proposed traditional indications. These properties can be connected to 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.

Annex