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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 (traditional use)

Draft – Revision 1

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 1:0.65-0.93) 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). Dry extract (DER 6-9:1), extraction solvent water. Dry extract (DER 5-10:1), extraction solvent water.
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use Herbal preparations in liquid or solid dosage forms for oral use. Comminuted herbal substance for infusion preparation for cutaneous use.
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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Achillea millefolium* L., herba
	Barbara Tóth (revision)
Peer-reviewer	Marie Heroutová

Note: This draft assessment report is published to support the public consultation of the draft updated European Union herbal monograph on *Achillea millefolium* L., herba. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft updated 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 updated monograph.

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1. Introduction

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

- Herbal substance(s)

According to the definition in the European Pharmacopoeia 9th ed. (2016), the herbal substance is the whole or cut, dried flowering tops of yarrow, *Achillea millefolium* L., and it should contain a minimum of 2 mL/kg essential oil (dried drug) and proazulenes, expressed as chamazulene ($C_{14}H_{16}$; M_r 184.3) a minimum of 0.02 percent (dried drug) (Ph. Eur. monograph ref.: 07/2014:1382).

- Herbal preparation(s)
    - Communited herbal substance as infusion for tea preparation
    - Expressed juice (1:0.65-0.93) from fresh herb
    - Liquid extract (1:1), extraction solvent: ethanol 25% (V/V)
    - Tincture (1:5) extraction solvent: ethanol 45% (V/V)
    - Tincture (1:5), extraction solvent ethanol 31.5% V/V)
    - Dry extract (DER 6-9:1), extraction solvent water.
    - Dry extract (DER 5-10:1), extraction solvent water.

Main active compounds

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.

The chemical composition the essential oil depends on the number of chromosomes present in the plant. Diploid and tetraploid plants contain proazulene sesquiterpenes, including chamazulene (up to 25%) and achillicin. Other major constituents of tetraploid species are β-pinene (23%), α-pinene (5%) and caryophyllene (10–22%). Hexaploid plants are azulene sesquiterpene-free, and contain approximately 50% of mono- and sesquiterpenes. Octaploid plants contain approximately 80% oxygen-containing monoterpenes (WHO 2009).

The essential oil of *A. millefolium* may contain α-thujone (0-26.6%) and β-thujone (0-11.0%) (Orav et al. 2006).

- 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.

Not applicable

1.2. Search and assessment methodology

The assessment report of *Millefolii herba* is based on the following literature resources using the term of Yarrow, *Achillea millefolium* L*.,* herba:

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).

- The term of Yarrow, *Achillea millefolium* L*.,* herb was searched.

Search engines used: Google

Scientific databases: PubMed (Using the Mesh term "*Achillea millefolium*" from 2011 to 10 September 2018), Embase (Using the term "*Achillea millefolium*" from 2011 to 10 September 2018),

Medical databases: Cochrane Database of Systematic Reviews (Using the term "*Achillea millefolium*" from 2011 to 10 September 2018)

Toxicological databases: ToxNet (December 2018)

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

Pharmacovigilance resources: EudraVigilance was searched on 11 September 2018.

Data from EU and non-EU regulatory authorities: Market overview provided by National Competent Authorities and EMA Article 57 product data

Other resources: Literature submitted by Interested Parties

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Millefolii herba, finely chopped herbal substance	Digestive, spasmolytic. Loss of appetite	3x3-4 coated tablets containing 190 mg each (corresponding to 3x570-760 mg herbal substance).	"Healing products" 1996-1997, Hungary)
Tincture of Millefolii herba (1:5), extraction solvent: ethanol 31.5% (V/V)	Gastrointestinal complaints like mild cramps, loss of appetite	Tincture >12 years: 4.3 ml (=4.2 g) tincture 4 times daily	WEU (at least since 1976, Germany) Healing product in Hungary 1995-2001

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		If the symptoms persist longer than 1 week or if they are recurrent or in case of unclear complaints, a doctor should be consulted.	
Millefolii herba, comminuted	Oral use: Loss of appetite, dyspeptic disorders like mild gastrointestinal cramps. External use: hip bath: Pelvipathia vegetativa	Herbal tea For drinking: 1.5 g/150 ml boiling water 3 times daily External use: added to bath water: 100 g/20 l If the symptoms persist longer than 1 week or if they are recurrent, a doctor should be consulted.	German Standard Marketing Authorisation (1986, Germany)
Expressed juice of fresh Millefolii herba (1:0.65-0.85)	Traditionally used for mild, spasmodic gastrointestinal complaints including bloating, and for loss of appetite.	Expressed juice >12 years: 10 ml 3 times daily If the symptoms persist longer than 2 weeks, a doctor should be consulted.	WEU, in 2012 switch to TUR (at least since 1976, Germany)
Expressed juice (1:0.65-0.85) from fresh Millefolii herba	Digestive complaints like mild spasms in the gastro-intestinal tract, loss of appetite.	3 times daily 5 ml liquid containing 100% expressed juice.	WEU (at least since 1976, Germany)
Expressed juice (1:0.84-0.93) from fresh Millefolii herba, oral liquid	Digestive complaints like mild spasms in the gastro-intestinal tract, loss of appetite.	2 times daily 10 ml liquid containing 100% expressed juice.	WEU (at least since 1990, already authorised in the former GDR, Germany)
Dry extract of Millefolii herba (5-10:1), extraction solvent water	Traditional herbal medicinal product for the symptomatic treatment of minor spasm associated with menstrual periods.	Film-coated tablet 250 mg Women and girls over 12 years of age: 1 2-3 times daily If the symptoms persist longer than 1 week, a doctor should be consulted.	TUR (07/2018, Germany)
Dry extract of Millefolii herba (6-9:1), extraction solvent water	Traditional herbal medicinal product for the symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating,	Instant herbal tea >12 years: 1 bag (1.2 g) containing 334 mg dry extract dissolved in 200 ml hot or cold water 3-4 times daily	TUR (01/2019, Germany)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	and flatulence.	If the symptoms persist longer than 2 weeks, a doctor should be consulted.	
Millefolii herba	Mild gastrointestinal complaints and symptomatic treatment of cramps during menstruation.	Herbal tea 1.2 g per tea bag Adults and adolescents: 3-4 x daily 1 tea bag as infusion If no improvement within 14 days ask a doctor.	THMP (05.2011, Austria)
Millefolii herba, comminuted herbal substance		Herbal tea, infusion. Herbal tea, infusion bags 1.0 g	National registration IL-3109/LN (Poland [")
Millefolii herba, comminuted herbal substance	Orally: In transient lack of appetite; gastrointestinal disorders like bloating and flatulence; in mild spasmodic menstruation disorders For topical use: in mild skin injuries for compresses.	For oral use: In lack of appetite and in gastrointestinal disorders an infusion of 3.6g (two sachets) drink 3-4 times a day, between meals. In menstruation disorders an infusion of 1.8 g one sachet) in a glass of water drink 2-3 times daily. For topical use: In mild skin injuries a fresh infusion of 3.6 g (two sachets) use for compresses, 2-3 times daily.	National registration IL-2743/LN (28.09.1990, Poland)
Millefolii herba, comminuted herbal substance	Traditional herbal medicinal product used in: lack of appetite. mild spastic gastrointestinal disorders like flatulence; symptomatic mild spastic menstruation complaints; topically in minor skin injuries	Herbal tea, infusion, infusion bags 2.0 g. In lack of appetite and gastrointestinal disorders an infusion of 2-4 g (1-2 sachets), drink 3-4 times a day, between meals. If the symptoms persist longer than 2 weeks, consult a doctor. In menstruation disorders	TUR, IL-1025/LN, (22.11.1993, Poland)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		an infusion of 2 g in a glass (250ml) of water drink 2-3 times daily. If the symptoms persist longer than 1 week during the use of product, consult a doctor. For external, use in mild skin injuries a fresh infusion of 4 g (two sachets) use 2-3 times a day for compresses. If the injury not heal in a week of use of the compresses please consult a doctor.	
Millefolii herba, comminuted herbal substance	Traditional herbal medicinal product used in: lack of appetite; mild gastrointestinal disorders; mild spastic menstruation complaints; topically in minor skin injuries	Herbal tea, infusion bags 1.5g. For oral uses. In lack of appetite and flatulence an infusion of 3 g (two sachets) drink 3-4 times a day, half an hour before meals. In gastrointestinal disorders, the same prepared infusion drink 3-4 times a day between meals. In menstruation disorders an infusion of 1.5g one sachet) in a glass of water drink 2-3 times daily. For topical use. In mild skin injuries, a fresh infusion of 3 g (two sachets) use 2-3 times daily for compresses.	National registration IL-6148/LN (Poland)
Millefolii herba, comminuted herbal substance	Traditional herbal medicinal product used in: lack of appetite. mild spastic	Herbal tea, infusion, infusion bags 2.0g. In lack of appetite and gastrointestinal	TUR, IL-3343/LN (Poland)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	gastrointestinal disorders like flatulence; symptomatic mild spastic menstruation complaints; topically in minor skin injuries	disorders an infusion of 2-4g (1-2 sachets), drink 3-4 times a day, between meals. If the symptoms persist longer than 2 weeks, consult a doctor. In menstruation, disorders an infusion of 2g in a glass (250ml) of water drink 2-3 times daily. If the symptoms persist longer than 1 week during the use of product, consult a doctor. For external use in mild skin injuries a fresh infusion of 4 g (two sachets) use 2-3 times a day for compresses. If the injury not heal in a week of use of the compresses please consult a doctor.	
Millefolii herba	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.	Czech Republic, 1997 - 2010
Herbal substance (Millefolii herba) as herbal tea	Traditional herbal medicinal product for treatment loss of	Oral use: (infusion) 3.5 g of herbal substance in ½ glass of bolding	Poland, more than 30 years.

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	appetite and dyspeptic complaints (mild, spastic gastrointestinal discomfort). Topical use: small superficial epidermal excoriation.	water 2–3 times daily. Topical use: Infusion should be prepared the same way.	

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

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

Czech Republic

1) Žaludeční čajová směs

Herbal tea containing Absinthii herba 300 mg, Millefolii herba 300 mg, Menthae piperitae herba 300 mg, Levistici radix 150 mg, Hyperici herba 150 mg, Liquiritiae radix 150 mg, Foeniculi fructus 150 mg in one tea bag

Indication: a) temporary loss of appetite, b) mild dyspeptic/gastrointestinal disorders

Posology: 1 tea bag (1.5 g)/250 ml of boiling water/10 min three times daily after meal

On the market since 1995.

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

No information available.

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

No information available.

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

According to Blumenthal et al. (2000), yarrow has been used as medicine by many cultures for hundreds of years (Budavari 1996; Zeylstra 1997). 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 (Todd 1967),
- British Herbal Pharmacopoeia (BHP) 1974, 1996,
- 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),
- Polish Herbal Compendium (1978),
- Potter's New Cyclopaedia of Botanical Drugs and Preparations (Wren 1988).

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. 1996, 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).

Herbal preparations:

- In the literature: Comminuted herbal substance as infusion for tea preparation (Kern 1969, Hänsel et al. 1992, BHP 1974, , Augustin et al. 1948, Rácz et al. 1984, German Commission E monograph 1990, Wren 1988, Bisset 1994, Newal et al. 1996, Bradley 1992, ,)
- 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)

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
Comminuted herbal substance as infusion for tea preparation	Temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	Oral use Three times daily: 2-4 g	Todd 1967, Bradley 1992, Hänsel et al. 1992
		Oral use Daily dose: 4.5 g of yarrow herb Single dose: Hot water (ca. 150 ml) are poured over two spoonful (2-4 g) and after 10 min. through a tea strainer, three or four times daily between meals	Bisset 1994.
		Infusion: 1-2 g in 150 ml boiled water for 10-15 minutes, three times daily between meals	Blumenthal 2000
		Oral use Single dose: 2 teaspoons (2-4 g, or 1.5 g based on ÖAB90) of Millefolii herba in 150 mL boiling water 3-4 times a day.	Kern 1969.
Liquid extract (DER: 1:1), extraction solvent:	Temporary loss of appetite and mild,	Oral use 2-4 ml three times daily	Wren 1988, Bradley 1992, Newal et al.

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
ethanol 25% (V/V)	spasmodic gastro-intestinal complaints including bloating, and flatulence.		1996, BHP 1974.
Tincture (ratio of herbal substance to extraction solvent: 1:5), extraction solvent: ethanol 45% (V/V)	Temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	Oral use 2-4 ml three times daily	Bradley 1992, Newal et al. 1996, BHP1974.
Comminuted herbal substance as infusion for tea preparation	Spasm associated with menstrual periods.	Oral use 1-2 g comminuted herbal substance in 250 ml boiling water as a herbal infusion 2-3 times daily	Madaus 1938, Fintelmann and Weiss 2002

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Comminuted herbal substance as a herbal infusion	Temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	2-4 g of the comminuted herbal substance in 250 ml boiling water as an herbal infusion 3 or 4 times daily between meals.	At least since 1976, Germany More than 30 years, Poland Todd 1967
Dry extract of Millefolii herba (6-9:1), extraction solvent water	Traditional herbal medicinal product for the symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	Instant herbal tea >12 years: 1 bag (1.2 g) containing 334 mg dry extract dissolved in 200 ml hot or cold water 3-4 times daily	TUR (01/2019, Germany)
Expressed juice of fresh Millefolii herba (1:0.65-0.85)	Traditionally used for mild, spasmodic gastrointestinal complaints including bloating, and for loss of appetite.	Expressed juice >12 years: 10 ml 3 times daily If the symptoms persist longer than 2 weeks, a doctor should be consulted.	WEU, in 2012 switch to TUR (at least since 1976, Germany)
Expressed juice (1:0.65-0.85) from fresh Millefolii herba	Digestive complaints like mild spasms in the	3 times daily 5 ml liquid containing 100% expressed	WEU (at least since 1976, Germany)

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	gastro-intestinal tract, loss of appetite.	juice.	
Expressed juice (1:0.84-0.93) from fresh Millefolii herba, oral liquid	Digestive complaints like mild spasms in the gastro-intestinal tract, loss of appetite.	2 times daily 10 ml liquid containing 100% expressed juice.	WEU (at least since 1990, already authorised in the former GDR, Germany)
Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V	Temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	Oral use 2-4ml three times daily	BHP 1974
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V	Temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	2-4 ml 3 times daily	BHP1974
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 31.5% V/V	Temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence.	4.3 ml (= 4.2 g) 4 times daily	At least since 1976, Germany
Comminuted herbal substance as a herbal infusion	Minor spasms associated with menstrual period	1-2 g comminuted herbal substance in 250 ml boiling water as a herbal infusion 2-3 times daily	Madaus 1938 and TUR products in Poland
Dry extract of Millefolii herba (5-10:1), extraction solvent water	Traditional herbal medicinal product for the symptomatic treatment of minor spasm associated with menstrual periods.	Film-coated tablet 250 mg Women and girls over 12 years of age: 1 2-3 times daily	TUR (07/2018, Germany)
Comminuted herbal substance for infusion preparation for cutaneous use	Small superficial epidermal excoriation	3-4 g of comminuted herbal substance in 250 ml water 2-3 times daily	More than 30 years, Products in Poland
Millefolii herba, comminuted	External use: hip bath: Pelvipathia vegetativa	External use: added to bath water: 100 g/20 l	German Standard Marketing Authorisation (1986, Germany)

Millefolii herba (comminuted herbal substance, expressed juice and tincture) has been used in several EU member states in the treatment of temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence at least since 1976.

Liquid extract (DER: 1:1), extraction solvent: ethanol 25% (V/V) of Millefolii herba has been used for temporary loss of appetite and mild, spasmodic gastro-intestinal complaints including bloating, and flatulence (BHP 1974).

Madaus have recommended Millefolii herba as herbal tea for the treatment of minor spasms associated with menstrual period since 1938 and products can be found on the Polish market as well.

Comminuted herbal substance as herbal infusion has been used to treat small superficial epidermal excoriations in Poland for more than 30 years.

Assessor's comment: The comminuted herbal substance was also used as hipbath to treat pelvipathia vegetative in Germany since 1986; but this indication is not considered appropriate for the monograph. The plausibility of this indication questionable. 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.

The following indications was accepted for the European Union Monograph on Millefolii herba:

Indication 1)

Traditional herbal medicinal product used for temporary loss of appetite.

Indication 2)

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

Indication 3)

Traditional herbal medicinal product for the symptomatic treatment of minor spasm associated with menstrual periods.

Indication 4)

Traditional herbal medicinal product for the treatment of small superficial wounds.

The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

Preparations in the monograph

Based on the products on the market or in the literature for more than thirty years:

- Comminuted herbal substance as a herbal infusion
- Dry extract of Millefolii herba (6-9:1), extraction solvent water*
- Dry extract of Millefolii herba (5-10:1), extraction solvent water*
- Expressed juice from fresh herb (DER 1:0.65-0.93)**
- 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

Assessor's comment:

**The two dry extracts prepared with water as solvent were accepted for the monograph since they can be considered the dried forms of the infusion. (See Q&A of the HMPC "Regulatory Q&A on herbal medicinal products" (EMA/HMPC/345132/2010 – Rev. 4)*

***Expressed juice from fresh herb (DER 1:0.65-0.85) and Expressed juice from fresh herb (DER 1:0.84-0.93) were combined in the monograph.*

The posology in the monograph

Adolescents, adults and elderly.

Oral use:

Indications 1) and 2):

a) Herbal tea: 2-4 g of the comminuted herbal substance in 250 ml boiling water as an 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 2):

f) Dry extract (DER 6-9:1), extraction solvent water: 334 mg dry extract 3-4 times daily

Indication 3):

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

g) Dry extract (DER 5-10:1), extraction solvent water: 250 mg dry extract 2-3 times daily

Cutaneous use:

Indication 4):

a) Comminuted herbal substance for infusion preparation for cutaneous use: 3-4 g of the comminuted herbal substance in 250 ml water 2-3 times daily.

Note: The posology in the monograph covers dosage of all Polish preparations.

The use in children under 12 years of age is not recommended.

Assessor's comment: The use of the comminuted herbal substance in adolescents was accepted taking into consideration that adolescents have used the expressed juice traditionally for more than 30 years. There are no safety concerns since an herbal tea preparation contains assumingly a similar or rather lower amount of ingredients. 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

3.1.1. Primary pharmacodynamics

***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).

- 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 o**f *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.

In vivo studies

- Anti-inflammatory effect

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 (70 ºC) 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).

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Strength Dosage Route of administration	Experimental model In vivo/ In vitro	Reference Year of publication	Main non-clinical conclusions
Hot (70 ºC) water extract (yield 36%, approximately DER:	100 or 300 mg/kg/day for 7 days, orally	*in vivo*	Cavalcanti et al. 2006	Oral pre-treatment of rats with the

Herbal preparation tested	Strength Dosage Route of administration	Experimental model In vivo/ In vitro	Reference Year of publication	Main non-clinical conclusions
2.8:1) from the aerial part of yarrow (*Achillea millefolium* L.)				extract one hour before induction of acute gastric lesions by ethanol had a dose-dependent protective effect.
Dry 80% ethanolic extract from the aerial parts of yarrow	100 mg/kg, orally	*in vivo*	Mascolo et al. 1987	Inhibited oedema in the carrageenan-induced rat paw oedema test by 29% ($p<0.05$) compared to 45% by indometacin at 5 mg/kg. ($p<0.01$)
Lyophilized cold water extract of yarrow herb	0.2 mg/ml	*in vitro*	Tunón et al. 1995	Inhibited the PAF-induced exocytosis of elastase from human neutrophils. Inhibited the biosynthesis of prostaglandins from ^{14}C-arachidonic acid.
70%-methanolic extract of the aerial parts of *Achillea millefolium* (DER: 5.5:1)	0.3-10 mg/mL	*in vitro*	Yaeesh et al. 2006	Concentration-dependent spasmolytic activity.
Methanolic [20% (V/V)] lyophilized extract (DER:2.75:1) of powdered aerial parts of *Achillea millefolium* L., and two fractions enriched in flavonoids and dicaffeoylquinic acids (DCQAs).	various concentrations	*in vitro*	Benedek et al. 2007 (b)	The extract and the fractions inhibited HNE, and MMP-2 and -9.
Water soluble	various concentrations	*in vitro*	Trouillas et al. 2003	Inhibitory effects in

Herbal preparation tested	Strength Dosage Route of administration	Experimental model In vivo/ In vitro	Reference Year of publication	Main non-clinical conclusions
fraction of a hydro-alcoholic extract of *Achillea millefolium.*				soybean 15-lipoxygenase assay.
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%).	various concentrations	*in vitro*	Benedek et al. 2006	Dose-dependent increase in bile flow.
Flavonoid fraction of yarrow, and its main flavonoids as well as quercetin and two flavonoid metabolites	various concentrations	*in vitro*	Lemmens-Gruber et al. 2006	Spasmolytic activity of the flavonoid fraction, the glycosides and respective aglycones.

3.1.2. Secondary pharmacodynamics

In vitro

- 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).

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 an 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 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).

- 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 (Stojanović 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).

- 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 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 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- cannot be defined on this basis (Innocenti et al. 2007).

- 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**

- 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.

The aqueous extract (AE) was prepared by infusion of the flowers of the plant (3 × 30 min) in water at 70 ◦C (1:10, w/v). The infusion was filtered and concentrated under vacuum (at 56 ◦C) to 1/12 of the original volume and stored at -20 ◦C. The concentrated extract (yield 36%) was diluted in distilled water immediately before use.

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).

- 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).

- 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 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).

3.1.3. Safety pharmacology

- 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).

Assessor's comment: The clinical relevance of these results is not known. The effects of Millefolii herba on the electrocardiogram, cardiac enzymes and serum electrolytes were studied after intravenous administration, which is not comparable to the oral or cutaneous routes of administration accepted in the Monograph on Millefolii herba.

- Effect on blood pressure

Dry hydroethanolic (ethanol 90%) extract (yielding 17.39%) and semi-purified fractions, and artemetin obtained from dried and powdered aerial parts of *A. millefolium* reduced the blood pressure of rats, after oral administration (100 mg/kg-300 mg/kg, p.o.) (de Souza et al., 2011).

The crude (spissum) hydromethanolic (methanol 70%) extract of dried aerial part of *Achillea millefolium* (Am.Cr) (yielding 18%) caused a dose-dependent (1–100 mg/kg i.v.) fall in arterial blood pressure (BP) of rats under anaesthesia. In spontaneously beating guinea-pig atrial tissues, Am.Cr exhibited negative inotropic and chronotropic effects. In isolated rabbit aortic rings, Am.Cr relaxed phenylephrine and high K^+ -induced contractions. This study shows that *Achillea millefolium* exhibits BP-lowering, cardio-suppressant, vasodilator and bronchodilator activities, mediated possibly through Ca^{++} antagonism in addition to an endothelium dependent relaxant component (Khan and Gilani, 2011).

Assessor's comments: The clinical relevance of these results is not known. However, in the study conducted by de Souza et al., the applied doses were significantly higher than those accepted in the Monograph on Millefolii herba (de Souza et al., 2011). In the study of Khan and Gilani, the blood pressure lowering effects of Millefolii herba were observed after intravenous administration, which is not comparable to the oral or cutaneous routes of administration accepted in the Monograph on Millefolii herba.

3.1.4. Pharmacodynamic interactions

Subchronic exposure to aqueous extract of leaves from *Achillea millefolium* (AE) on enzyme- and non-enzyme-dependent antioxidant systems was investigated in rats. Administration of AE (1 g/kg/twice a day, p.o.) for 7 days increased by 73% the glutathione (GSH) levels in uterus and decreased it by 23% in kidneys without altering the amounts of GSH in liver. In preliminary experiments targeting the interaction of AE with acetaminophen (600 mg/kg, p.o.), the augmentation of acetaminophen-induced increase of plasmatic alanine aminotransaminase, aspartate aminotransaminase and lactate dehydrogenase was observed. The authors concluded that the results indicate a potential toxic interaction of AE compounds with xenobiotics that use the glutathione pathway (e.g. acetaminophen). Further investigation is needed to fully assess the potential toxicity of A. millefolium in interaction of other xenobiotics such as acetaminophen (Baggio at al., 2015).

3.1.5. Conclusions

Available non-clinical data support the plausibiliy of the traditional use of Millefolii herba for the symptomatic treatment of mild, spasmodic gastro-intestinal complaints, minor spasm associated with menstrual periods, loss of appetite and small superficial wounds.

None of the reported pharmacological studies constitute any cause for safety concern.

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

3.3.1. 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 10 g/kg orally or 1 and 3 g/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* L.) at 3 g/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 1 g/kg (Anonymous 2001).

3.3.2. Repeat 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).

3.3.3. Genotoxicity

The mutagenic activity of dry extract from yarrow (Millefolii herba Ph. Eur., extraction solvent water, DER: 6-9:1) was examined in bacteria with and without the addition of a mammalian metabolic activation system. Six concentrations, 70, 221, 700, 2212, 7000 and 8536 µg of the dry extract from yarrow per plate was examined in the five Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 in two independent experiments, each carried out without and with metabolic activation (a microsomal preparation derived from Aroclor 1254-induced rat liver). The first experiment was carried out using a plate incorporation method and the second using a preincubation method. No signs of cytotoxicity were noted in any experiment without and with metabolic activation up to the top concentration of 8536 µg dry extract from yarrow/plate in any test strain. Dry extract from yarrow up to a concentration 8536 µg/plate caused no mutagenic effect in the Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 neither in the plate incorporation test nor in the preincubation test, each carried out without and with metabolic activation (LPT report, 2015).

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 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 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 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).

3.3.4. Carcinogenicity

No information available.

3.3.5. Reproductive and developmental toxicity

Yarrow has been used as an abortifacient, as an emmenagogue, to cure amenorrhea as a contraceptive and for stimulating uterine contractions by primitive societies. There has been, however, little scientific research carried out to either confirm or refute these reports (Boswell-Ruys et al. (2003).

In the study of Boswell-Ruys et al. (2003), female rats were administered orally, by gavage, 2.8 g/kg body weight/day (i.e. 56 times the human dose, the recommended human dose is 50 mg/kg/day) of ethanolic solution of a commercial **yarrow** extract on either gestation days (GD) 1-8 or GD 8-15.. The extract of yarrow used consisted of the dried aerial parts of the yarrow plant (not including the flowers) extracted in 45% ethanol in a 1:2 dilution, giving a final concentration of 500 mg/ml. The stock was diluted with water to 20% w/v to minimize risk of damage of alcohol to the gastrointestinal tract.

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. .

The influence of alcohol present in the yarrow preparation must be considered a factor in the reduced fetal weight. Alcohol treatment alone (1.98 g/kg/day GD 8–15), however, did not significantly reduce fetal weight. This contrasts with Samson et al. (1979) who reported a reduced fetal weight after administration 2 g/kg/day to rats on GD 9–12. The possibility remains that the observed effects in the yarrow-treated rats may be a result of the additive effect of alcohol and yarrow.

Authors concluded that a 2.8 g/kg body weight daily dose of yarrow was associated with reduced foetal weight and increased placental weight. According to the authors in the absence of a no observable

effect level for these variables it must be concluded that the consumption of yarrow is contraindicated during pregnancy until further investigations have been carried out (Boswell-Ruys et al. (2003).

Assessor's comment: This finding is not relevant for the monograph, the plant part is not the same (aerial part but without flowers), comparing to the traditionally used ethanolic extract the preparation in this article has different ratio of herbal substance to extraction solvent (1:2, not 1:5).

Another study (Dalsenter et al. 2004) evaluated the toxicity of the exposure to the aqueous extract from **leaves o**f *Achillea millefolium* L. on reproductive endpoints in Wistar rats. The plant material was dried at room temperature and extracted (10%, W/v) with water (100 g/3 l) at 70 °C and concentrated under vacuum to 1/12 of the original volume (56 °C). 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. The daily sperm production as well as the number of sperms in the cauda epididymis were also unaffected, suggesting absence of adverse effects on the spermatogenic process.

The treatment with the highest dose of yarrow aqueous extract altered the sperm morphology of Wistar rats. Although the percentage of abnormal sperm (3.1%) was statistically different in the group treated with the highest dose of yarrow extract, these numbers are under the expected percentage of abnormalities in Wistar rats (up to 5%). Furthermore, a 3-day treatment of immature female rats did not show any uterotrophic effects (Dalsenter et al. 2004).

*Assessor's comment: The result of the study shows that the aqueous extract of A. millefolium **leaves** administered to adult male rats did not have (anti)estrogenic activity in vivo at the dose levels tested.*

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).

Assessor's comment: No conclusion on the human use of yarrow can be drawn from this study. The hydro-alcoholic extract is not characterised adequately, the method of administration is not in accordance of the traditional use (intraperitoneal, not oral).

Nicotine (NIC) adversely influences male reproductive system. A study was conducted to assess whether Achillea millefolium (Achm) **inflorescences alcoholic extract** could serve as a protective agent against reproductive toxicity in NIC-exposed male rats. The alcoholic extract of dried inflorescences of the plant was prepared by infusion of the finely dried material in methanol 70%, at 20 °C (1:10, w/v) for 36 hr. Adult male rats were randomly divided into six groups. Two groups received NIC at doses of 0.20 and 0.40 mg kg-1 per day in 0.50 mL sterile distilled water for 48 days intraperitoneally, respectively. The further two groups received NIC at doses of 0.20 and 0.40 mg kg-1 per day in 0.50 mL sterile distilled water for intraperitoneally along with Achm extract at a dose of 1.20

g kg-1 per day in 1 mL sterile distilled water orally for 48 days, respectively. A vehicle treated control group and an Achm-only treated group were also included. The NIC-exposed groups showed significant reductions in epididymal sperm count, motility, viability and serum levels of FSH, LH and testosterone as well as testicular antioxidant capacity. Moreover, the incidence of apoptosis and abnormality in spermatozoa along with testicular malondialdehyde and total nitrite levels were significantly higher in NIC-treated rats. The above-mentioned parameters were restored to near normal levels by Achm co-administration. These findings indicated that Achm might partially be protective against NIC-induced testicular toxicity (Hasanzadeh et al. 2017).

Assessor's comment: No conclusion on the human use of yarrow can be drawn from this study. The method of administration is not in accordance of the traditional use (intraperitoneal, not oral).

3.3.6. Local tolerance

No information available.

3.3.7. Other special studies

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 sensitizer. Other known yarrow constituents like dehydromatricaria ester and pontica epoxide appear to play no role.

3.3.8. Conclusions

The available toxicological data do not show any harmful effect of yarrow (*Achillea millefolium* L.):

No toxic symptoms over the observational period of 14 days were observed in a rat study 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 orally or 1 and 3 g/kg intraperitoneally (Cavalcanti et al. 2006).

In the same study, rats were treated with the same extract 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. No sign of relevant toxicity was observed.

The Ames test was performed with dry extract from yarrow (Millefolii herba Ph. Eur., extraction solvent water, 70% native extract, ratio of herbal drug to drug preparation: 6-9:1) in the five Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537. No signs of mutagenicity were noted in any experiment without and with metabolic activation.

No test on carcinogenicity have been performed.

Three experimental studies on embryotoxicity and reproductive toxicity demonstrate relatively marginal effects. Oral use of 2.8 g/kg body weight daily dose of an ethanolic extract of the **aerial part of yarrow without flowers** (56 times the human dose) was associated with reduced foetal weight and increased placental weight in female rats. There was no difference in incidence of external or internal malformations. Administration of 1.2 g/kg/day of aqueous **yarrow leaves** extract during 90 days by oral gavage altered the sperm morphology of Wistar rats. Although the percentage of abnormal sperm (3.1%) was statistically different in the group treated with the highest dose of yarrow

extract, these numbers are under the expected percentage of abnormalities in Wistar rats (up to 5%). The daily sperm production as well as the number of sperms in the cauda epididymis were not affected, suggesting absence of adverse effects on the spermatogenic process.

It can be concluded that animal studies are insufficient with respect to reproductive toxicity. The tests were performed with different parts of the plants, at more fold higher doses therefore, the results of these studies cannot be considered adequate to assess the reproductive toxicity of yarrow herb.

Guinea pig sensitisation tests performed with the whole plant indicated some sensitisation potential for yarrow extracts and one sesquiterpene lactone component.

3.4. Overall conclusions on non-clinical data

The above mentioned pharmacological studies made the proposed indications plausible.

It is suggested that yarrow works in three ways, reflecting the different properties of its constituents: sesquiterpene lactones to stimulate digestive and immune function; achillein as an antimicrobial and anti-inflammatory agent; and azulene to reduce inflammation (O'Donnell, 1999).

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 Deutsches Arzneinuch (1997).

Non-clinical data on coleretic, gastroprotective, spasmolyticand anti-inflammatory effects support the traditional use as an infusion for the symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating and flatulence.

Non-clinical data on spasmolytic and analgesic activity support the traditional use as an infusion for the symptomatic treatment of minor spasm associated with menstrual periods.

Non-clinical studies on anti-inflammatory activity may make the wound healing effect plausible.

Specific data on pharmacokinetics are not available.

The available toxicological (single dose and repeat dose toxicity) data do not show any harmful effect of yarrow (*Achillea millefolium* L.)

Animal studies are insufficient with respect to reproductive and developmental toxicity, so the use during pregnancy and lactation cannot be recommended.

Tests on genotoxicity support the safety of Millefolii herba. The Ames test was performed with dry extract from yarrow (Millefolii herba Ph. Eur., extraction solvent water, 70% native extract, ratio of herbal drug to drug preparation: 6-9:1); therefore, it can support the establishment of a European Union list entry for dry yarrow extract made with water and comminuted herbal substance

No test on carcinogenicity have been performed.

4. Clinical Data

4.1. Clinical pharmacology

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

Oil yarrow extracts demonstrated significant anti-inflammatory effect in a double-blind randomized study with 23 volunteers on artificially irritated skin by the application of 8% sodium lauryl sulfate (SLS). The extracts were prepared from the aerial parts of yarrow using olive oil or sunflower oil (drug/extract ratio: 1:5). Skin parameters assessed in the study (skin capacitance, pH and erythema

index) were restored to the basal values after three- and seven-day treatment with the tested extracts, and the effects could not be attributed to the oils itself (Tadić et al., 2017).

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

No information available.

4.2. Clinical efficacy

4.2.1. Dose response studies

No information available.

4.2.2. Clinical studies (case studies and clinical trials)

Until now, no clinical studies investigated the effects of orally administered Millefolii herba. However, the topical effect of Millefolii herba was evaluated in a placebo-controlled study performed by Hajhashemi et al. (2018). The purpose of this study was to assess the efficacy of Achillea millefolium and Hypericum perforatum ointments on episiotomy wound healing in 140 primiparous women. They were randomly divided into four groups, each group containing 35 women: 2 control groups including non-intervention and placebo ointment; and 2 case groups including Hypericum perforatum ointment and Achillea millefolium ointment.

Each plant was broken separately, and then extracted using 90% ethanol solution. The acquired hydroalcoholic extract was dried and these dry extracts in a form of ointment with sterile vaseline as base (% 5 weight ratio) were packed in 30 g tubes. Vaseline without extract was used as placebo.

Healing process was assessed by five specifications: redness, ecchymosis, edema, discharge and wound dehiscence on 7th, 10th, and 14th days after delivery; pain level was assessed by means of visual analog scale.

In terms of pain severity at day 2 after the labour, there was no significant difference between the groups. However, at days 7, 10 and 14, a significant difference was observed between the groups ($p<0.05$), hence the ointments of *Achillea millefolium* and *Hypericum perforatum* were more effective than placebo ointment and non-intervention groups in reducing pain severity. Moreover, *A. millefolium* and *Hypericum perforatum* ointments were more effective in reducing redness, oedema and ecchymosis of episiotomy wound ($p<0.05$) compared to placebo. Evaluating dehiscence and secretion of the wounds revealed no significant difference between the groups ($p>0.05$).

Table 5: Clinical studies on humans, in skin inflammations

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Comments on clinical relevance of results
To evaluate the efficacy of oil extracts of Millefolii herba in treatment of topical/dermatological skin impairments. Tadić et al., 2017	Double-blind, randomised, placebo-controlled	Olive oil or sunflower oil extracts of yarrow (E1-E4), DER 1:5, used topically twice a day for 7 days	23	Healthy, normal skin with no signs of dermatological diseases	Effects of the investigated yarrow extracts on skin capacitance, skin pH value, and erythema index evaluated after 3 and 7 days of treatment.	Three-day application of extracts E3 and E4 led to the improvement of skin hydration; this effect was, however, not registered in case of extracts E1 and E2. The application of sample E4, after a three-day and a seven-day application, led to significantly higher hydration in relation to the untreated control (UCO). After only three days of yarrow herb oil extracts application (samples E1-E4), the pH values of the skin of the subjects were not significantly different compared to basal values, indicating a positive effect of oily extracts on the buffer capacity of the skin. However, on the 7th day of the treatment, compared to UCO, a significantly different pH value was recorded after treatment with the extracts E3 and E4. After the three-day application of oil extracts E1 and E2 a significant decline in EI was registered compared to UCO, to the value not differing from the basal values. The same trend for	Patient population is not properly described. High risk of selection and performance biases are suspected. The applied doses of the extracts are not given. The tested product is not comparable to any preparations listed in the Monograph.

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Comments on clinical relevance of results
						these samples (E1 and E2) was observed after 7 days of treatment, as well. For samples E3 and E4 after a three-day application there was no significant difference of EI compared to basal values. The seven-day application lead to lower EI vales but in the case of sample E3, as well as in the case of sample E4, these values were higher compared to basal values, the registered increase being not statistically significant. However, after 7-day treatment with these samples, recorded EI value was significantly lower compared to UCO.	

Table 6: Clinical studies on humans, in wound healing

Type	Study	Test Product(s)	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Comments on clinical relevance of results
To evaluate the episiotomy wound healing effects of *A. millefolium* ointments. Hajhashemi et al., 2018	Double-blind, randomised, placebo-controlled	*A. millefolium* ointments containing 90% ethanolic extract in vaseline base, 5% weight ratio were applied from the second day after delivery. The patients were asked to rub 1 cm of the ointment on the area of episiotomy, twice a day for 10 days.	A total of 140 women were enrolled; based on the exclusion criteria, 134 subjects were retained, among them 35 subjects were included in the non-intervention group, 34 in the placebo ointment group, 32 in the *Achillea millefolium,* ointment group, and 33 in the *Hypericum perforatum* ointment group.	Primiparous women Inclusion criteria: no history of the diseases that disrupt wound-healing process, and no history of allergy to herbal medicines, no active skin diseases. Exclusion criteria: third and fourth degree perineal rupture; prolonged rupture of membranes.	Evaluating episiotomy pain was done based on the VAS scale. Redness, oedema and ecchymosis of episiotomy wound. Dehiscence and secretion of the wounds.	Episiotomy pain: 2 days after the labour there was no difference, however, at days 7, 10 and 14, a significant difference was observed between the groups ($p<0.05$) favouring *A. millefolium* and *Hypericum perforatum* ointments over placebo. *A. millefolium* and *Hypericum perforatum* ointments were more effective in reducing redness, oedema and ecchymosis of episiotomy wound ($p<0.05$) compared to placebo. Evaluating dehiscence and secretion of the wounds revealed no significant difference between the groups ($p>0.05$).	Only 32 patients applied *A. millefolium* ointment. The tested product is not comparable to any preparations listed in the Monograph.

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

Elderly

According to the provided literature, no clinical studies have been conducted with Millefolii herba alone in elderly.

Children

According to the provided literature, no clinical studies have been conducted with Millefolii herba alone in children.

Pregnancy

The use of Millefolii herba has not been evaluated in pregnant women.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no published clinical studies on Millefolii herba where the active substance of the medicinal product has been in medicinal use within the EU for at least ten years. Well-establish use in accordance with Article 10a of Directive 2001/83/EC is considered not fulfilled for Millefolii herba.

5. Clinical Safety/Pharmacovigilance

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

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 Asteraceae-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 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 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 Asteraceae 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).

Clinical trials performed with Yarrow (Tadić et al., 2017 and Hajhashemi et al. 2018) do not mention any undesirable effect.

5.2. Patient exposure

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

5.3. Adverse events, serious adverse events and deaths

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 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 millefolium*), 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 information available.

5.5. Safety in special populations and situations

No information available.

5.5.1. Use in children and adolescents

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

5.5.2. Contraindications

Hypersensitivity to yarrow and other Asteraceae species (Blumenthal et al. 1998, 2000, Bradley 1992, Hänsel et al. 1992, Newal et al. 1996).

5.5.3. Special Warnings and precautions for use

For indication 1), 2) and 3): If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

For 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.

5.5.4. Drug interactions and other forms of interaction

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).

No drug interactions and other forms of interaction were reported.

5.5.5. Fertility, pregnancy and lactation

Yarrow 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. However, 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. A daily dose of 2-4 g three times daily 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 health (see Public statement on the use of herbal medicinal products containing thujone EMA/HMPC/732886/2010).

According to Newal excessive use should be avoided during lactation (Newal et al. 1996). However, this statement is not supported by any clinical data. Therefore, 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.

No fertility data are available.

5.5.6. Overdose

No case of overdose has been reported.

5.5.7. 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.

5.5.8. Safety in other special situations

Not applicable

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 family” was included in the 4.3. Contraindication section of the European Union herbal 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.

6. Overall conclusions (benefit-risk assessment)

There are no published clinical studies on Millefolii herba where the active substance of the medicinal product has been in medicinal use within the EU for at least ten years. Well-establish use in accordance with Article 10a of Directive 2001/83/EC is considered not fulfilled for Millefolii herba.

The traditional medicinal use of yarrow herb has been documented in several medicinal handbooks with indications consistent with the existing pertinent pharmacological experiments performed *in vitro* and *in vivo* and it is substantiated by the presence of medicinal products on the European market.

The traditional use of yarrow preparations (*Achillea millefolium* L., herba*)*) fulfils the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2004/24/EC as amended. All the requirements for traditional use (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety) are met.

The following preparations and indications are proposed for the European Union monographs:

- comminuted herbal substance,
- expressed juice from fresh herb (DER: 1:0.65-0.93),
- liquid extract (DER 1:1), extraction solvent ethanol 25% V/V,

- tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V,
- tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 31.5% V/V),
- dry extract (DER 6-9:1), extraction solvent water,
- dry extract (DER 5-10:1), extraction solvent water

Indication 1)

Traditional herbal medicinal product used for temporary loss of appetite.

Indication 2)

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

Indication 3)

Traditional herbal medicinal product for the symptomatic treatment of minor spasm associated with menstrual periods.

Indication 4)

Traditional herbal medicinal product for the treatment of small superficial wounds.

The therapeutic areas for browse search with traditional use indications are:

- loss of appetite
- gastrointestinal disorders
- urinary tract and genital disorders
- skin disorders & minor wounds

As a general precaution related to the therapeutic indications, the product information should include a warning text advising the patient to consult a doctor or a qualified health care practitioner if the symptoms persist longer than 2 week during the use of the product for indications 1) and 2) and 1 week for indications 3) and 4).

Millefolii herba cannot be recommended for oral use in children under 12 years of age due to lack of adequate data.

If patients with known hypersensitivity to yarrow herb and other plants of Asteraceae family are excluded, a traditional use in adolescents and adults is considered safe from a clinical point of view. The benefit-risk balance can be considered positive.

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

No data on fertility is available.

Adequate tests on reproductive toxicity has not be performed.

No tests on carcinogenicity have been performed.

Adequate test on genotoxicity is available for the dry extract (DER 6-9:1; extraction solvent: water). Results of the genotoxicity test are considered applicable to other water preparations included in the

EU monograph, i.e. herbal tea for oral use, infusion preparation for cutaneous use and dry extract (DER 5-10:1).

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

The data on safety are considered sufficient to support a European Union list entry for the following herbal preparations:

- Comminuted herbal substance,
- Dry extract (DER 6-9:1), extraction solvent water
- Dry extract (DER 5-10:1), extraction solvent water

for the following indications:

- Traditional herbal medicinal product used for temporary loss of appetite,
- Traditional herbal medicinal product for the symptomatic treatment of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence,
- Traditional herbal medicinal product for the symptomatic treatment of minor spasm associated with menstrual periods,
- Traditional herbal medicinal product for treatment of small superficial wounds.

Annex

List of references