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EMA/HMPC/680595/2013
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Agrimonia eupatoria* L., herba

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

Draft

Herbal substance (binomial scientific name of the plant, including plant part)	<i>Agrimonia eupatoria</i> L., herba
Herbal preparations	a) Comminuted herbal substance b) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V) c) Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for infusion preparation or decoction preparation for oromucosal use, cutaneous use or as a bath additive. Herbal preparations in liquid dosage forms for oral use or oromucosal use.
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Assessor(s)	L Anderson

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



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1. Introduction

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

- Herbal substance

Agrimonia eupatoria L., herba

Definition of the herbal substance

The definition of *Agrimoniae herba* in the current European Pharmacopoeia 7th edition is "Dried flowering tops of *Agrimonia eupatoria* L. Content: minimum 2.0% of tannins, expressed as pyrogallol (C₆H₆O₃; M_r 126.1) (dried drug).

Principal constituents of the herbal substance

Constituents reported in *Agrimonia eupatoria* include tannins (mainly ellagitannin and procyanidins and a wide variety of flavonoids among which luteolin, apigenin, quercetin and kaempferol derivatives have been reported as major compounds: (Bradley, 1992; Blaschek *et al.* 1998; ESCOP, 2009). A comprehensive study of the polyphenolic constituents (Granica *et al.* 2013) has provided a more detailed evaluation of *Agrimoniae herba*.

Tannins

3-11% consisting mainly of proanthocyanidins (condensed tannins) with a small proportion of ellagitannins. The proanthocyanidins are present mainly in the form of leucoanthocyanins which yield cyanidin on acid hydrolysis: procyanidin trimer, procyanidin B3 (Granica *et al.* 2013)

Acids

Palmitic acid, salicylic acid, silicic acid and stearic acid.

Flavonoids

Ca. 1.9%, principally hyperoside (0.37%), together with rutin, isquercitrin, quercitrin, , isovitexin; apigenin, its 7-*O*-glucoside, 7-*O*-β- D-glucuronide, ; kaempferol, its 3-glucoside, 3-rhamnoside, 3-rutinoside, 7-*O*-β- D-glucuronide, malonyl hexoside, hexoside, 4'- methyl ether (kaempferide),kaempferide 3-rhamnoside; luteolin, its glucuronide isomer, 7-*O*-glucoside, 7-*O*-glucuronide; quercetin, its 3-*O*-rhamnoside, rhamnoglucoside isomer, malonyl hexoside isomers (Sendra and Zieba, 1972; Carnat *et al.* 1991; Bilia *et al.* 1993 a; Bilia *et al.* 1993 b; Granica *et al.* 2013).

Triterpenoids

Ursolic acid (0.6%); also euscaptic acid and the 28-glucosylesters of euscaptic acid and tormentic acid (Le Men and Pourrat 1955).

Phenolic acids

Chlorogenic, caffeic and ellagic acids; also p-hydroxybenzoic, protocatechuic, homoprotocatechuic, gentisic, vanillic, salicylic, p-coumaric, ferulic acids, 3-*O*-p-coumaroylquinic acid, 4-*O*-caffeoylquinic acid, 5-*O*-caffeoylquinic acid (Granica *et al.* 2013)

Minerals

7.3-7.9% with a relatively high silica content. Potassium and sodium concentrations in the dried herb: reported as 12,882 micrograms/g and 37.2 micrograms/g, respectively.

Vitamins

Ascorbic acid (vitamin C), nicotinamide complex (about 100–300 µg/g leaf), thiamine (about 2 µg/g leaf) and vitamin K.

Volatile oil

Cedrol, α -pinene, linalool, α -terpineol, bornyl acetate, eucalyptol (major constituents; Feng *et al.* 2013).

Other constituents

β -sitosterol, polysaccharides, unidentified coumarins.

Herbal preparation(s)

Information about products on the market in the Member States

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following herbal preparations have been on the European market:

Herbal preparations which have been reported to be marketed under traditional use:

Member State	Medicinal Product (Mono Preparation)	Regulatory Status
Germany	German Standard Marketing Authorisation single active ingredient: 1 herbal tea <i>Indications:</i> Internal use: mild unspecific acute diarrhoea, inflammations of the oropharyngeal mucosa; External use: mild superficial inflammations of the skin <i>Posology:</i> Oral use: 2 to 4 times daily one cup of tea-infusion; Oromucosal use: gargle with the infusion (infuse 1.5 g herbal substance with 150 ml boiling water for 10 to 15 minutes); Cutaneous use: several times daily compresses (boil 10 g herbal substance with 100 ml cold water for several minutes and then filter)	since 1976
Czech Republic	<i>Indications:</i> Oral use: as a mild astringent in mild unspecific diarrhoea and a as a choleric in minor gastrointestinal disturbances Oromucosal use: for treatment of minor inflammations in oral cavity and pharynx	since 1997; 1999

	<p>Cutaneous use: for treatment of minor superficial skin inflammations</p> <p><i>Posology:</i> Oral use: infusion as a herbal tea; 1 tea spoon (1.5 g)/250 ml of boiling water/15 minutes, 2-3 times daily</p> <p>Oromucosal or cutaneous use: decoction 2 – 3 tea spoons (3 – 4.5 g) boil for 10 minutes with 250 ml of boiling water+15 minutes; use several times daily as a gargle, for compresses or as a bath additive</p>	
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Pharmacopoeias, handbooks

British Herbal Pharmacopoeia	<p>Powdered herb by infusion Posology: 3 times daily 2 – 4 g</p> <p>Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V) Posology: 3 times daily 2 – 3 ml</p> <p>Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V) Posology: 3 times daily 1 – 3 ml</p>	1976
Czech Pharmacopoeia	<p>Oral use: single dose 1.5 g; daily dose 3.0 – 4.5 g; Local use: single dose 3.0 – 4.5 g</p>	1976
Commission E	<p>Oral use: dried herb as infusion Posology: 3 times daily 1-3 g</p> <p>External: 10% decoction, in compresses 2-3 times daily.</p>	

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.

According to the overview of the market Agrimony herb is used in combination with other herbal substances/herbal preparations. No detailed information about the combination substances and indications is available.

In the Czech Republic, combination preparations and tea preparations of Agrimony herb are on the market. The following combination products are registered in the Czech Republic:

- 1) Herbal tea containing Calami radix, Angelicae radix, Matricariae flos, Centaurii herba, Hyperici herba, Agrimoniae herba, Menthae piperitae herba, Rubi fruticosi folium, Foeniculi fructus - on the market since 1969, for oral use, indications - used as stomachicum, carminativum, the product has mild spasmolytic, antiphlogistic and choleric effect
- 2) Herbal tea containing Agrimoniae herba, Marrubii herba, Boldo folium, Taraxaci radix cum herba, Frangulae cortex, Matricariae flos, Menthae piperitae herba – on the market since 1996, for oral use, indications - adjuvant therapy in biliary tract disorders

- 3) Herbal tea containing Agrimoniae herba, Marrubii herba, Menthae piperitae herba, Rhei radix – on the market since 1997, for oral use, indications – adjuvant therapy in mild gastrointestinal disorders, loss of appetite and mild functional biliary tract disorders

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Croatia					food supplements only
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Germany	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	since 1976
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	homeopathic medicinal prod.; food supplements
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	no prod. on the market
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	combination prod. only

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

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

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

1.2. Search and assessment methodology

A literature search was performed in September 2013 using the common databases of the DIMDI database information system (e.g. MEDLINE, EMBASE, SciSearch, Cochrane Library). Additional searches were carried out on published books on herbal medicines and plant monographs.

2. Historical data on medicinal use

2.1 Information on period of medicinal use in the Community

Agrimony herb has a long history of use as a medicinal plant. The following extensive uses are reported (Duke, 1985):

Said to alleviate condylomata, sclerosis of the spleen and liver, tumours of the internal organs, mesenteric region, scrotum, sinews, and stomach, as well as corns and warts, and cancer of the breast, face, mouth and stomach. Reported to be astringent, cardiotoxic, coagulant, depurative, diuretic, emmenagogue, litholytic, sedative, tonic vermifuge and vulnerary. Used as a folk remedy for asthma, bronchitis, dermatitis, entorrhagia, enuresis, gastrorrhagia, hematuria, hepatitis, metrorrhagia, neuralgia, neuritis, pharyngitis, rheumatism, tuberculosis and warts. Astringent, the herb tea is useful for internal bleeding, and/or looseness of the bowels. Has a great reputation for curing jaundice and other liver ailments. Recommended for snakebite, gout, skin eruptions, pharyngitis, diseases of the blood, blotches, pimples etc. Febrifugal and vermifugal; used for tapeworm. The plant is gargled for inflammation of the throat and mouth. Mixed with fat, it is used as a poultice to draw out indolent ulcers.

The following list shows examples of the many herbal books, pharmacopoeias and standard reference publications with monographs on Agrimony herb.

<i>English Herbal</i> (Salmon, 1710)	To stop bleeding, dry up catarrh, dropsy. Dose half to one dram at night.
<i>British Herbal</i> (Hill, 1751)	For opening obstructions to the viscera and for jaundice.
<i>The British Flora Medica</i> (Barton & Castle, 1877)	Infusion as a tea considered valuable for liver complaints and skin eruptions. A very good gargle for sore throats. Applied to sprains it was esteemed efficacious.
<i>A Modern Herbal</i> (Grieve, 1931)	Astringent, tonic; useful in coughs, diarrhoea and relaxed bowels. An infusion or decoction is an excellent gargle for a relaxed throat and for looseness of the bowels (3-4 times daily).
<i>Medicinal Plants and their uses</i> (Fluck, 1971)	Internally as a tisane (1 litre of cold water to a handful of drug, raise to boil: for diarrhoea, biliary retention and inflammation of the bladder and kidneys. Externally its infusion is used as a lotion for inflamed mucosa of the mouth and throat and as an application to wounds.
<i>The Complete German Commission E Monographs</i> (Blumenthal, 1998)	Internal use: mild non-specific acute diarrhoea. Inflammation of the oral and pharyngeal mucosa.

	External use: mild, superficial inflammation of the skin.
<i>British Herbal Compendium</i> (Bradley, 1992)	<p>Mild diarrhoea, especially in children. Cutaneous porphyria.</p> <p>As a gargle for the oral and pharyngeal mucosa including acute sore throat and chronic pharyngeal catarrh.</p> <p>External use: skin disorders, including inflammation, rashes, sores, eruptions and ulcers and wound healing.</p> <p>Internal use: three times daily, 1-3g dried herb or as an infusion or equivalent preparation; liquid extract (1:1) in 25% ethanol, 1-3 ml. Tincture (ratio of herbal substance to extraction solvent 1:5) in 45% ethanol, 5-10ml.</p> <p>External use: 10% decoction, in compresses several times daily.</p>
<i>Herbal Drugs and Phytopharmaceuticals</i> (Wichtl, 2004).	<p>Mild astringent, internally and externally, for inflammation of the throat, gastroenteritis and for intestinal catarrh.</p> <p>Tea preparation: 1.5 g dried herb into cold water and boil or pour boiling water over the herb.</p> <p>For bowel disorders: 1 cup tea 2-3 times daily. Use tea as a gargle or for rinsing mouth.</p>
<i>Medicaments a base de plantes (Ministere de la Sante et de L'action Humanitaire, 1990)</i>	<p>Traditionally used:</p> <p>Orally and for cutaneous use: in subjective manifestations of venous insufficiency, such as heavy legs, and for haemorrhoidal symptoms.</p> <p>Traditionally used for mild diarrhoea.</p> <p>Traditionally used in mouthwashes, for oral hygiene.</p>
<i>Potter's New Cyclopedia of Botanical Drugs and Preparations</i> (1971)	<p>Mild astringent, tonic, diuretic, deobstruent.</p> <p>Useful in coughs, simple diarrhoea and relaxed bowels.</p> <p>1 oz of the dried herb infused in 1 pint of boiling water, sweetened with honey or sugar and taken in frequent doses of half a cupful.</p>
<i>Encyclopedia of Herbal Medicine</i> (Bartram, 1995)	<p>Weak acid stomach, indigestion, sluggish liver and debility, gall bladder disorders, nose-bleed, sore throat, laryngitis (gargle), bed-wetting, incontinence, diarrhoea, to promote flow of gastric juices.</p> <p>Local: ulceration – to cleanse and heal; ancient remedy for suppurating sores and wounds.</p> <p>Tea: 3 times daily, 1 teaspoon herb in cup of boiling water. Liquid extract (1:1; 25% ethanolic) 1-3ml</p> <p>Tincture (ratio of herbal substance to extraction solvent 1:5 45% ethanolic) 1-4 ml.</p>

Based on pharmacopoeias and standard text books of herbal medicine for Agrimony herb, the requirement for a period of at least 30 years of medicinal use, from Directive 2004/24/EC, for qualification as a traditional herbal medicinal product, is fulfilled.

According to the information provided by the National Competent Authorities in the overview of the marketed products and the CZ P and BHP, qualification as a traditional herbal medicinal product is fulfilled for:

- a) Comminuted herbal substance
- b) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V)
- c) Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)

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

For the herbal substance and preparations thereof the following indications are described in pharmacopoeias and literature:

Gastric disorders:

Mild, nonspecific, acute diarrhoea	Commission E (1998)
Diarrhoea in children, mucous colitis	BHP (1976), BHP (1983)
Mild diarrhoea	ESCOP (2009)
Mild diarrhoea, especially in children.	Bradley (1992)

Oral and pharyngeal disorders:

Gargle for acute sore throat, chronic nasopharyngeal catarrh.	BHP (1976), BHP (1983)
Inflammation of oral and pharyngeal mucosa	Commission E(1998)
Gargle for inflammation of oral and pharyngeal mucosa	ESCOP (2009)

Cutaneous

Mild, superficial inflammation of the skin	Commission E(1998)
As a compress or rinse to support wound healing	ESCOP (2009)

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following indications are found:

Germany

- oral use for mild unspecific acute diarrhoea

- as a gargle for - inflammations of the oropharyngeal mucosa
- cutaneous use as a compress/bath additive for– mild superficial skin inflammations

Czech Republic

- oral use – as an mild astringent in mild unspecific diarrhoea and as a choloretic in minor gastrointestinal disturbances
- oromucosal use as a gargle – for treatment of minor inflammations in oral cavity and pharynx
- cutaneous use as a compress or as a bath – for treatment of minor superficial skin inflammations

Based on literature and indications for marketed products, the following indications are proposed for the monograph:

Indication 1)

Traditional herbal medicinal product for the symptomatic relief of mild diarrhoea.

Indication 2)

Traditional herbal medicinal product used as a gargle for the symptomatic relief of minor inflammations of the mouth and throat.

Indication 3)

Traditional herbal medicinal product for relief of minor skin inflammation and small, superficial wounds.

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

The following references provide evidence for the traditional medicinal use:

Posology

Herbal substance for tea preparation, infusion & decoction

References	Dosage	Mode of Administration
Commission E	Posology: 3 times daily 1-3 g External: 10% decoction, in compresses 2-3 times daily.	Tea preparation for oral , oromucosal use. Decoction for cutaneous use
Czech Pharmacopoeia	Two- three times daily: 1.5 g	Tea preparation for oral , oromucosal use
BHP (1976) BHP (1983)	three times daily: dried herb, 2-4 g by infusion	Oral , oromucosal use
For the monograph the following dosage is recommended taking account of preparations marketed in MS: Herbal tea: 1.5 -4 g of the comminuted herbal substance in 250 ml (or less) of boiling water as a		

herbal infusion, 2- 4 times daily for oral use.

Comminuted herbal substance for infusion preparation: 1.5 g of the comminuted herbal substance in 150 ml of boiling water , 2 – 4 times daily as a gargle

Comminuted herbal substance for decoction preparation: 3 – 4.5 g of the comminuted herbal substance in 250 ml (or less) of boiling water, as a decoction 2 – 3 times daily as a gargle

Comminuted herbal substance for decoction preparation: 3-10 g of the comminuted herbal substance in 100 ml 250 ml (or less) of water as a decoction. Apply as an impregnated dressing to the affected areas of the skin

Comminuted herbal substance for decoction preparation: 3-10 g of the comminuted herbal substance in 250 ml (or less) of water, twice daily. Use as a bath additive up to 30 minutes twice daily.

Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)

References	Dosage	Mode of Administration
BHP (1976)	Three times daily: 2 – 3 ml	Oral, oromucosal,
BHP (1983)	Three times daily: 1 – 3 ml	Oral, oromucosal,
Bradley (1992)	Three times daily: 1- 3 ml	Oral, oromucosal,

For the monograph the following dosage was considered:

Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V): 1-3 ml 3 times daily

Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V)

References	Dosage	Mode of Administration
BHP (1976)	Three times daily: 1–3 ml	Oral, oromucosal,
BHP (1983)	Three times daily: 1–4 ml	Oral, oromucosal,

For the monograph the following dosage was considered:

Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V): 1-4 ml 3 times daily

Route of administration

Agrimony preparations have been used traditionally by oral, oromucosal and cutaneous routes of administration.

Duration of use

No information on the duration of use is available. In order to assure safe use as a traditional herbal medicinal product within the scope of the simplified traditional use registration scheme, the duration of use is adapted to take account of the therapeutic indications:

Indication 1)

Traditional herbal medicinal product for the symptomatic relief of mild diarrhoea.

If the symptoms persist **longer than 3 days** during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indications 2) and 3)

Traditional herbal medicinal product for use as a gargle for the symptomatic relief of minor inflammations of the mouth and throat.

Traditional herbal medicinal product for relief of minor skin inflammation.

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

3 Non-Clinical Data

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

Primary pharmacodynamics

Anti-microbial activity

Marked antibacterial activity against *Staphylococcus aureus* and α -haemolytic streptococci has been reported for agrimony (Petkov, 1986).

Anti-inflammatory activity

A hydroethanolic extract (2.5 g drug/100ml ethanol 50% V/V) of agrimony showed strong elastase-inhibiting activity (Lamaison *et al.* 1990).

Anti-oxidant effects

An infusion from 1 g of agrimony in 200 ml of water had considerable antioxidant activity. In relation to the reactivity of Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) as a standard, the Trolox equivalent antioxidant capacity (TEAC) was 3.76mM (Ivanova *et al.* 2005).

Other effects of possible relevance to the proposed indication(s)

A dry 50%-methanolic extract from agrimony exhibited no spasmolytic activity on spontaneous or induced contractions of isolated guinea-pig ileum at concentrations up to 800 µg/ml (Izzo *et al.* 1996).

In the rat, following oral administration of agrimony infusions and decoctions (15% w/v), diuretic activity was minimal and elimination of urea unchanged. Further experiments in the rat showed that, while diuresis resulting from distilled water provoked loss of electrolytes, agrimony compensated for electrolyte loss, particularly that of potassium). (Giachetti *et al.* 1989).

Secondary pharmacodynamics

A hypotensive effect in anaesthetised cats has been documented for an agrimony extract given by intravenous injection; blood pressure was lowered by more than 40% (Petkov, 1979).

Significant uricolytic activity has been documented for agrimony infusions and decoctions (15% w/v), following their oral administration to male rats at a dose of 20 mL/kg body weight (equivalent to 3 g dry drug) (Giachetti *et al.* 1986).

An aqueous ethanol extract of the herb was tested for immunomodulative activity in the peritoneal cavities of mice (Bukovsky and Blanarik, 1994). Immunostimulant activity resulted in an increase in phagocytic activity and increases in the activities of lysozyme and peroxidase.

Agrimonia eupatoria given in the diet of mice for 12 days prior to intraperitoneal administration of streptozotocin resulted in a reduction in hyperglycaemia (Swanston-Flatt *et al.* 1990). Further investigation revealed stimulation of 2-deoxyglucose transport, glucose oxidation and incorporation of glucose into glycogen in mouse abdominal muscle. An aqueous extract (0.25–1 mg/mL) stimulated insulin secretion from a BRIN-BD11 pancreatic B cell line (Gray and Flatt, 1998). These findings demonstrate that *A. eupatoria* aqueous extract given orally to mice has antihyperglycaemic, insulin-releasing and insulin-like activity (Gray and Flatt, 1998).

An aqueous extract of the aerial parts of *A. eupatoria* inhibited the secretion of hepatitis surface antigen in an *in vitro* system using HepG2.2.15 cells, which produce complete virion particles and viral proteins (Kwon *et al.* 2005).

Studies in related species

The related species, *A. pilosa*, has been investigated in a number of studies. Particular interest has been shown in the tannin agrimoniin. Until recently this constituent had not been reported in *A. eupatoria*.

Several phloroglucinols isolated from *A. pilosa* have demonstrated activity against *Staphylococcus aureus*, and a methanol extract of the herb inhibited HIV-1 protease activity (Yamaki *et al.* 1994; Min *et al.* 1999).

In vivo antitumour activity in mice has been attributed to the tannin agrimoniin (Miyamoto *et al.* 1985). Agrimoniin was administered intraperitoneally into ascites-type and solid tumours in rodents (Miyamoto *et al.* 1987). At doses of greater than 10 mg/kg, given before or after intraperitoneal inoculation with MM2 cells, it completely rejected tumour growth in mice (Miyamoto *et al.* 1987). Solid tumours of MH134 and Meth-A were inhibited by agrimoniin, and the number of peripheral blood cells was increased, indicating that agrimoniin has antitumour activity and that it exerts its effect by enhancing the immune response. *In vitro* studies have reported that agrimoniin induces the cytotoxicity of murine peritoneal exudate cells and that it induces interleukin 1 in human peripheral blood mononuclear cells and in mouse adherent peritoneal exudate cells *in vivo* (Miyamoto *et al.* 1988; Murayama *et al.* 1992).

An aqueous suspension of *A. pilosa* herb (1 mg/kg and 5 mg/kg), given orally or intraperitoneally, significantly reduced blood glucose concentrations in streptozotocin-induced diabetic rats (Hsu and Cheng, 1992). The relevance of this observation to human is unknown.

Safety Pharmacology

No information available.

Pharmacodynamic interactions

No information available.

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

No published data are available.

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

Single dose toxicity/ repeat-dose toxicity

No studies have been reported.

Reproductive and developmental toxicity

No studies have been reported.

Genotoxicity

In an Ames test, using *Salmonella typhimurium* strains TA98 and TA 100 with and without metabolic S9 mix activation, no evidence of mutagenicity was observed for a commercial tincture (1:5, ethanol 70%) and a methanolic extract (Schimmer *et al.* 1994; Bilia *et al.* 1993).

The data presented on mutagenicity are incomplete, are not in accordance with current guidelines and do not cover the preparations proposed in the monograph.

3.4 Overall conclusions on non-clinical data

The information available on non-clinical studies is very limited.

No published data on pharmacokinetics are available.

No data from investigations concerning single- and repeat-dose toxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from Agrimony herb in animals.

Limited information is available on genotoxicity and the published studies are not sufficient. The requirements for a Community list entry are therefore, not fulfilled.

No studies have been undertaken with the aim of identifying constituents responsible for the effects of Agrimony preparations in animals or humans. The characteristic compounds of Agrimony herb are the tannin constituents, consisting mainly of proanthocyanidins (condensed tannins) with a small proportion of ellagitannins. Tannin-containing herbal preparations, in general, have traditional uses in the treatment of diarrhoea and for the relief of inflammation in the mouth and throat. The tannin constituents are therefore considered to contribute to the activity of Agrimony herb. However, studies confirming that these constituents are responsible for the therapeutic activity of Agrimony preparations in humans are currently lacking.

4 Clinical Data

4.1 Clinical Pharmacology

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

No data available.

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

No data available.

4.2 Clinical Efficacy

4.2.1 Dose response studies

Dose response studies have not been performed.

4.2.2 Clinical studies (case studies and clinical trials)

One clinical study has been located in the literature. Patients with cutaneous porphyria (n=20) were treated orally with an infusion of Agrimony 3-4 times daily before meals (4 teaspoon of crushed herb to 1 liter of water).

After 15 days substantial improvements in skin eruptions were observed together with decreases in serum iron levels and urinary porphyrins. All patients were stated to have showed improvements in general health (appetite, lack of dyspepsia and regularity) (Patrascu *et al.* 1984). The methodological limitations of this small, uncontrolled study do not allow any conclusions to be made on the effects of agrimony. In addition, use for cutaneous porphyria would require medical supervision so this use is considered as outside the scope of the traditional registration scheme.

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

No data from clinical studies in children or elderly are available.

4.3 Overall conclusions on clinical pharmacology and efficacy

The information available on clinical studies is very limited.

Only one small clinical study was located with a mono-preparation of Agrimony. This study is not sufficient to support Agrimony as a well-established medicinal product with recognised efficacy and acceptable safety.

However, the traditional use of Agrimony is well documented in literature including standard herbal reference books and it is included in a number of European pharmacopoeias. A small clinical study has been reported in patients with cutaneous porphyria, however, this use would require medical supervision so it is considered as outside the scope of the traditional registration scheme. The efficacy of agrimony products is considered plausible on the basis of long-standing use and experience for the administration in adolescents, adults and the elderly for the following indications which are considered within the scope of the THMPD:

Indication 1)

Traditional herbal medicinal product for the symptomatic relief of mild diarrhoea.

Indication 2)

Traditional herbal medicinal product for use as a gargle for the symptomatic relief of minor inflammations of the mouth and throat.

Indication 3)

Traditional herbal medicinal product for relief of minor skin inflammation and small, superficial wounds.

5. Clinical Safety/Pharmacovigilance

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

See chapter 4.1.1.

5.2 Patient exposure

There is no information available on the extent of use.

5.3 Adverse events and serious adverse events and deaths

General data:

No adverse events, serious adverse events and deaths are reported.

Case reports in the Member States:

No adverse events have been reported by Member States during the preparation of the monograph.

Published case reports:

No adverse events are reported in the literature.

5.4 Laboratory findings

No data available.

5.5 Safety in special populations and situations

Use in children, adolescents

No clinical studies have been reported in children.

Due to the lack of sufficient data, the use is not recommended for children under 12 years of age. Use in adolescents is considered acceptable based on the indications and the short term treatments.

Contraindications

Hypersensitivity to the active substance is the only specified contraindication.

Special warnings and precautions for use

For indication 1) In order to ensure safe use the specific warning is included that if recurrent diarrhoea or bloody stools occur, a doctor or a qualified health care practitioner should be consulted.

In addition, to ensure safe use the duration of use is adapted to take account of the therapeutic indications:

Indication 1)

Traditional herbal medicinal product for the symptomatic relief of mild diarrhoea.

If the symptoms persist **longer than 3 days** during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indications 2) and 3)

Traditional herbal medicinal product for use as a gargle for the symptomatic relief of minor inflammations of the mouth and throat.

Traditional herbal medicinal product for relief of minor skin inflammation.

Special warnings and precautions for use are included:

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

Drug interactions and other forms of interaction

None reported. Experimental studies in mice show limited evidence of a possible blood glucose lowering effect of an Agrimony extract; however, there are no reported cases of interactions.

Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. There are no human data on the effects of Agrimony preparations on the foetus or on fertility.

In view of the absence of sufficient clinical data, the use of Agrimony products during pregnancy and lactation is not recommended.

Overdose

No cases reported.

Drug abuse

There are no reports of drug abuse with Agrimony preparations.

Withdrawal and rebound

There are no reports of withdrawal from Agrimony preparations.

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

No studies on the ability to drive and use machines have been performed. There are no reports on impairment of mental ability.

5.6 Overall conclusions on clinical safety

The information available on clinical studies is very limited. However, on the basis of the long-standing traditional uses there is no evidence to indicate that *Agrimonia eupatoria* is harmful in the specified conditions of use as summarised in the Table below. Due to lack of safety data, the use is not recommended for children under 12 years of age or during pregnancy and lactation.

Indication:	Symptomatic treatment of mild diarrhoea.	As a gargle for the symptomatic relief of minor inflammations of the mouth and throat.	Relief of minor skin inflammation and small, superficial wounds.
Preparation	a) Herbal tea: 1.5 – 4 g of the comminuted herbal substance in 250 ml (or less) of boiling water as a herbal infusion, 2-4 times daily.	a) Comminuted herbal substance for infusion preparation: 1.5 g of the comminuted herbal substance in 150 ml of boiling water 2 – 4 times daily as a gargle.	a) Comminuted herbal substance for decoction preparation: 3-10 g of the comminuted herbal substance in 250 ml (or less) of water. Apply as an impregnated dressing to the affected areas of the skin.
Preparation	b) Tincture: 1-4 ml, 3 times daily.	b) Comminuted herbal substance for decoction preparation: 3 – 4.5 g of the comminuted herbal substance in 250 ml (or less) of water, 2 – 3 times daily as a gargle.	b) Comminuted herbal substance for decoction preparation: 3-10 g of the comminuted herbal substance in 250 ml (or less) of water, twice daily. Use as a bath additive up to 30 minutes.
Preparation	c) Liquid extract: 1-3 ml, 3 times daily.	c) Tincture: 1-4 ml, 3 times daily as a gargle.	
Preparation		Liquid extract: 1-3 ml, 3 times daily as a gargle.	

6 Overall conclusions (benefit – risk assessment)

The available data do not support Agrimony herb as a well-established medicinal product with recognised efficacy and acceptable safety.

However, the traditional uses of Agrimony herb are accepted within the Member States, are well documented in literature including standard herbal reference books and the herbal substance/herbal preparations are included in a number of European pharmacopoeias.

The efficacy of Agrimony preparations is considered plausible on the basis of long-standing use and experience for the administration to adolescents, adults and the elderly for a number of indications considered within the scope of the THMPD.

The following traditional uses have been identified from the information available:

Indication 1)

Traditional herbal medicinal product for the symptomatic relief of mild diarrhoea.

Indication 2)

Traditional herbal medicinal product used as a gargle for the symptomatic relief of minor inflammations of the mouth and throat.

Indication 3)

Traditional herbal medicinal product for relief of minor skin inflammation and small, superficial wounds.

The indications fulfil the requirements for traditional use in that they are suitable for self-medication by routes of administration acceptable for traditional medicinal products. In addition, the specified preparations for traditional use have specified strength and posology.

The HMPC has concluded that:

No constituent with known therapeutic activity could be defined for the Agrimony preparations listed in the Monograph.

Tannin constituents serve as characteristic constituents for assay of the herbal substance (Ph Eur).

Flavonoid constituents (e.g. isoquercitroside, rutin) can also serve as analytical markers and are used as characteristic constituents for TLC identification of the herbal substance (Ph Eur).

An HMPC monograph can therefore be adopted based on traditional use only. However, because the minimum required data on mutagenicity (Ames test) are not available for the herbal preparations of Agrimony herb covered by the monograph, inclusion in the Community List of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.

Annex

List of references