EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Potentilla erecta* (L.) Raeusch., rhizoma

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Potentilla erecta* (L.) Raeusch. (*P. tormentilla* Stokes), rhizoma Syn: Tormentillae rhizome
Herbal preparation(s)	a) Comminuted herbal substance b) Tincture (1:5), extraction solvent ethanol 70% (V/V) [1] c) Tincture (1:5), extraction solvent ethanol 45% (V/V) d) Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V) e) Dry extract (DER 3.5-4.5:1), extraction solvent ethanol 60% (V/V)
Pharmaceutical forms	• Comminuted herbal substance as herbal tea for oral use. • Comminuted herbal substance for infusion or decoction preparation for oromucosal use. Herbal preparations b), c), d) and e) in liquid dosage forms for oral use. Herbal preparation b) in liquid dosage forms for oromucosal use.
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[1] The tincture complies with the Eur. Ph. monograph (ref.: 01/2008:1895).

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1. Introduction

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

- Herbal substance(s)

Tormentillae rhizoma consists according to the European Pharmacopoeia of the dried rhizome, freed from the roots of *Potentilla erecta* (L.) Raeusch. It contains not less than 7% of tannins, expressed as pyrogallol ($C_6H_6O_3$, Mr126.1) with reference to the dried herbal substance.
Tormentil (*Potentilla erecta* syn. *Tormentilla erecta*, *Potentilla tormentilla*) is an herbaceous perennial belonging to the rose family (*Rosaceae*).

Constituents (according to Hänsel & Sticher 2007, Blaschek at al. 2008, Wichtl 2009):

1. Tannins: 15-22% total tannins (15-20% condensed tannins, about 3.5% hydrolysable tannins)

- Condensed tannins: (−)- gallo- or (−)-epigallocatechingallat, the dimeric catechin derivatives [6,6']-all-trans-bi-(+)-catechin, [4,8]-all-trans-bi-(+)-catechin (= procyanidin B3), [4,6]-all-trans-bi-(+)-catechin (= procyanidin B6) and [4,8]-2,3-trans-3,4-cis-bi-(+)-catechin

- Hydrolysable tannins: After hydrolysis gallic acid and ellagic acid were found. The main compound of the hydrolysable tannins is agrimoniin, a dimeric ellagitannin, with a content of about 1% in the herbal substance. Further hexahydroxy diphenic acid, pedunculagin, laevigatin B and laevigatin F were isolated.

2. Flavonoids: kaempferol, cyanidinglucoside and leucoanthocyanidin and the tannin monomers catechin, epicatechin, gallocatechin and epigallocatechin

3. Phenol carboxylic acids: p-coumaric acid, 3,4-dihydroxybenzoic acid, gallic acid, sinapic acid and caffeic acid

4. Triterpene saponins: quinovic acid, tormentillic acid and tormentosid (glycoside of tormentillic acid)

5. Fatty acids: in extracts prepared with supercritical CO2 the following constituents are found: lauric acid, linoleic acid, linolenic acid, palmitic acid, palmitoleic acid, pentadecanoic acid, stearic acid and oleic acid.

- Herbal preparation(s)

The following herbal preparations are in medicinal use in the community for more than 30 years:

	Herbal preparation	**References**
a)	Comminuted herbal substance for preparation of infusions for preparation of decoctions (authorized products in Poland, on the market for more than 30 years)	Madaus 1938
b)	Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V)	Monograph in the Czech pharmacopoeia since 1970, monograph in the Austrian pharmacopoeia at least since 1960, replaced by the monograph in Ph. Eur. 01/2008:1895
c)	Tincture (ratio of herbal substance to extraction solvent	British Herbal Pharmacopoeia

	Herbal preparation	References
	1:5), extraction solvent ethanol 45% (V/V)	1974
D	Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)	British Herbal Pharmacopoeia 1974
E	Dry extract (DER 3.5-4.5:1), extraction solvent ethanol 60% (V/V)	Authorised product in Germany, on the market at least since 1976

Herbal preparations not considered in the monograph:

- Powdered herbal substance:
  Traditionally suspended in red wine for the treatment of acute unspecific diarrhoea (Wichtl 2009). Although the combination with tannins from red wine seems to be plausible this special pharmaceutical form does not seem to be suitable for THMPs. Weiß (1985) proposes a pinch of the powdered herbal substance several times daily. This posology seems to be too imprecise.

- Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 70% (V/V).
  This herbal preparation is mentioned only in recent editions of handbooks on phytotherapy (e.g., Jänicke et al. 2003, Kraft 2000). It seems that the authors refer in the proposed posology to the tincture (1:5).
  For the tincture (1:10) mentioned in the market overview of Spain no further information on extraction solvent and posology is available.

- 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.

Tormentillae rhizoma and its preparations are used with many other herbal substances or herbal preparations. This monograph refers only to Tormentillae rhizoma.

- Vitamin(s)

Not applicable.

- Mineral(s)

Not applicable.

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

The following information has been provided regarding monographs in national pharmacopoeias or products on the market with relevance for this monograph:

CZ:
Tormentillae radix has been a subject of Czechoslovak/Czech Pharmacopoeia since 1970; recommended dosage in the last version of the Czech Pharmacopoeia: single dose for oral use 1.5 g, daily dose for oral use 4.0–6.0 g.

Tormentillae tinctura (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V), has been a subject of Czechoslovak/Czech Pharmacopoeia since 1970; recommended dosage in the last version of the Czech Pharmacopoeia: single dose for local use 0.5-1.0 g.

DK:
The Danish Food Agency has accepted 200 mg *Potentilla erecta*, radix in a food supplement. This is not an upper limit but a specific assessment in a specific case.

LI:
The comminuted herbal substance is on the market for more than 30 years. The products are for the preparation of infusions for use in the proposed indications.

PL:
The comminuted herbal substance is on the market for more than 30 years. The products are for the preparation of decoctions for use in the proposed indications.

Regulatory status overview

Member State	**Regulatory Status**				**Comments**
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food supplements
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Food supplements
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combination only
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Combination only
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Tincture (1:10)

Member State	Regulatory Status				Comments
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No product

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.

1.3. Search and assessment methodology

Search terms: *Potentilla erecta*, *Potentilla tormentilla*, tormentil, Blutwurz

Databases: Pubmed, Medline and Toxnet

Libraries: University Vienna, center of pharmacy; Medical University Vienna, central library.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The medicinal use of Tormentillae rhizoma can be traced in literature back to the 15th century (according to Madaus 1938), it is also mentioned by Lonicerus and Matthiolus in the 17th century (cited in Benedum et al. 2006).

In fact, Tormentillae rhizoma has been in therapeutic use for many decades, a continuous use during the last 30 years is documented in the literature.
Therefore for Tormentillae rhizoma a period of at least 30 years in medicinal use as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product is easily fulfilled.

Type of tradition: European.

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

Tormentillae rhizoma is traditionally used for acute, unspecified diarrhoea, externally for haemostasis, mild inflammation of the oral and pharyngeal mucosa, prosthetic pressure points, frostbite, burns, haemorrhoids and poorly healing wounds (Madaus 1938, List & Hörhammer 1977, British Herbal Pharmacopoeia 1983, Weiß 1985, Blaschek et al. 2008, Fintelmann & Weiss 2002, Augustin & Hoch 2004).

Proposed indications for traditional use:

Indication 1)

Traditional herbal medicinal product for symptomatic treatment of mild diarrhoea.

Indication 2)

Traditional herbal medicinal product for the symptomatic treatment of minor inflammations of the oral mucosa.

Tormentillae rhizoma is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.
The high content of tannins makes the medicinal use in the proposed indication plausible.

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

Posology

Indication 1): Diarrhoea

	Herbal preparation	**Posology**
a)	Comminuted herbal substance for preparation of infusions	Corresponding 4-6 g herbal substance daily (authorised products in Lithuania for more than 30 years) 2-4 g 3 times daily (British Herbal Pharmacopoeia 1974)
	for preparation of decoctions	Corresponding 4-6 g herbal substance daily (German Commission E cited in Blumenthal 1998, Wichtl 2009) 2-3 g in 150–200 ml of water: drink 2 times daily (authorised products in Poland for more than 30 years)
b)	Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V)	30–50 drops in water, several times daily (Weiß 1985)
c)	Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V)	2-4 ml 3 times daily (British Herbal Pharmacopoeia 1974)
d)	Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)	2-4 ml 3 times daily (British Herbal Pharmacopoeia 1974)
E	Dry extract (DER 3.5-4.5:1), extraction solvent ethanol 60% (V/V)	3 times daily 2 capsules, each containing 200 mg dry extract

Indication 1): inflammations in the mouth or the throat

	Herbal preparation	**Posology**
a)	Comminuted herbal substance for preparation of infusions	Corresponding 4-6 g herbal substance daily (authorised products in Lithuania for more than 30 years)
	for preparation of decoctions	2-3 spoons (= 8-12 g) of the rhizome per litre of water. Rinse the mouth several times daily (Fintelmann & Weiss 2002)

	Herbal preparation	Posology
		Corresponding 4-6 g herbal substance daily (German Commission E cited in Blumenthal 1998, Wichtl 2009) 6 g in 200 ml water: for washing oral cavity (authorised products in Poland for more than 30 years)
b)	Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% (V/V)	1 teaspoon per glass of water, rinse the mouth (Fintelmann & Weiss 2002) 10-20 drops to one glass of water daily (Blumenthal et al. 1998)
c)	Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V)	No posology available, therefore not considered in the monograph in this indication
d)	Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)	No posology available, therefore not considered in the monograph in this indication
e)	Dry extract (DER 3.5-4.5:1), extraction solvent ethanol 60% (V/V)	Not authorised for this indication

Use in children:

There are no data from clinical trials or observational trials for the above mentioned herbal preparations available. Therefore the use should be restricted to adults.

The use of the dry extract was allowed in Germany for adolescents in case of unspecific acute diarrhoea.

Duration of use

Indication 1)
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.

Indication 2)
If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Method of administration

Indication 1)
Oral use.

Indication 2)
Oromucosal use.

3. Non-Clinical Data

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

Data obtained with traditional herbal preparations relevant for the proposed indications:

Antiviral effect
A decoction (DER 1:10) demonstrated antiviral activity in a plaque inhibition test against Herpes virus HVP 75 (type 2) and vaccine virus (May & Willuhn 1978).

Further data:

Astringent effect
Tannins as polyphenols exhibit the potential for so called multidentate interactions with other molecules, predominately with proteins. The binding on proteins may be irreversible (covalent binding) or reversible (hydrogen bonds). The astringency results from this affinity for proteins. Externally, they waterproof the external layers of the skin and mucosas, thus protecting the underlying layers; they also have a vasoconstrictor effect on small superficial vessels (Hänsel & Sticher 2007). Thus, the absorption of fluids from the intestinal lumen and the influx into this is reduced; the precipitate of the protein-tannin complex serves as a protective layer. The absorption of toxins is impeded; the effects of local irritants are reduced (Dingermann & Loew 2003). For most of these presumptions no experimental data are available.

Antimicrobial effects
Tannins exhibit antimicrobial effects independent of their plant source (Hänsel & Sticher 2007). A tannin complex isolated from Tormentillae rhizoma, which contained tannins, sugar and triterpenes, prevented fully the growth of the following bacteria, in the following concentrations: 2.5 mg/ml: *Pasteurella pseudotuberculosis*, *Shigella boydii*, *Shigella flexneri*, *Shigella sonnei*; 5 mg/ml: *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*; 10 mg/ml: *Escherichia coli* 055B5, *E. coli* 0111B4, *Streptococcus faecalis* (Pourrat et al. 1963 cited in Blaschek et al. 2008). The mentioned concentrations may be reached after consumption of a herbal tea of tormentil.

Antiinflammatory effect
Antiinflammatory properties are documented for a wide variety of tannins (Scholz 1994). Agrimoniin, major tannin of tormentil, was identified as a potent direct inhibitor of human neutrophil elastase with an IC_{50} of 0.9 µM (Hrenn et al. 2006).

Immunostimulatory effect
A weak immunostimulating effect was detected with a crude extract of tormentil prepared with water containing acetone (no details on the DER and the ratio water:acetone is provided). 25 mg crude drug extract per kg bodyweight was given intraperitoneally to mice. After an hour oxazolon was applied to the shaved belly of the animals for sensitization. After 7 days oxazolon was applied on one ear, which led to an average increase of the ear thickness by 24%. Substances causing an increase by 50%, were considered active by the authors. No further details are published regarding the number of mice or statistical parameters (Lund & Rimpler 1985).

Drozd and Anuszewska (2005) demonstrated that the combination of decoctions from ellagitannin containing pharmacopoeial raw materials (Cortex Quercus, Folium Uvae ursi and Rhizoma Tormentillae, decoction in usual concentration = approximately 2 g tormentil per 150 ml water) and the antibiotics cefuroxime, cefoperazone and doxycycline increases the survival of mouse thymocytes in cultures with supplementation of hydrocortisone. A cytotoxic test was used for the evaluation. The results showed

that each of the applied aqueous extracts caused a better survival of mouse thymocytes when added to the antibiotic in comparison to the antibiotic alone. The extract from Cortex Quercus showed the highest activation when added to the culture with cefuroxime. The best stimulation with cefoperazone was achieved when combined with the extract from Rhizoma Tormentillae. Doxycycline was most effective when combined with the extract from Folium Uvae ursi. The authors conclude that the combination of antibiotics and tannin raw materials could be advantageous for the immunological system of patients.

Assessor's comment:
The interpretation of the authors seems to be too optimistic. The conclusions made are far away from practical consequences and cannot be taken into account for the monograph.

Interferon inducing effect
A weak effect was observed in a study on interferon induction. Mice received 100 mg crude drug extract per kg bodyweight intraperitoneally. After 17 hours 0.05 ml of a dilution of Vaccinia-virus (IHD strain) was applied intravenously. This concentration produced untreated 12 to 25 separate lesions on the tail of each animal. Inhibition of these lesions on the eighth day by more than 50% is interpreted as a possible interferon inducing effect. The observed inhibition was approximately 28%. No further details are published regarding the number of mice or statistical parameters (Lund & Rimpler 1985).

Molluscicide effect
Aqueous and methanol extracts (5 g herbal substance in 100 ml) in concentrations of 400 ppm or 100 ppm are still active against the freshwater snail *Biomphalaria glabrata*, which is the intermediate host of schistosomiasis. The tannins are considered to be the molluscicide principle of the drug (Schaufelberger & Hostettmann 1983).

Hypoglycemic effect
Tormentic acid (isolated from the plant *Poterium ancistroides*, but also a constituent of tormentil) lowered in a concentration of 30 mg/kg body weight the fasting plasma glucose level with a corresponding increase in circulating insulin levels in rats. It also improved the glucose tolerance test by increasing insulin secretory response to glucose. Tormentic acid did not alter the insulin and glucose levels in streptozotocin-induced diabetic rats (Ivorra et al. 1988). Since no data on the concentration of tormentic acid in tormentil are available, the relevance of this publication for the use of tormentil cannot be assessed.

Antioxidant activity
Dimers and timers of procyanidins of tormentil displayed the highest anti-radical activity towards lipoperoxidation compared to other fractions of a water soluble tormentil extract. The IC_{50} of a total extract was determined with 0.024 mg/ml. Pentamers and hexamers possessed the most marked anti-elastase properties. The IC_{50} of a total extract was determined with 0.044 mg/ml. These effects are interpreted by the authors as a possible prevention of the aging effects of oxidative membrane impairment. No standard antioxidants were included for comparison of the results (Vennat et al. 1994, Bos et al. 1996).

Chandak et al. (2009) investigated pure gallotannin in rats with Streptozotocin (STZ)-induced diabetic nephropathy. Poly (ADP-ribose) polymerase (PARP) is known to be activated under conditions of oxidative stress and/or radiation exposure. Inhibition of PARP by specific inhibitors is known to prevent the development of STZ induced diabetic nephropathy by reduction in oxidative stress induced apoptosis. Gallotannin (20 mg/kg/day, i.p.) treatment for 4 weeks led to a significant reduction in the levels of plasma creatinine which is a well known marker for diabetic nephropathy. Treatment with gallotannin resulted in protection up to a certain level of glomerular damage, suggesting compensatory

glomerular hypertrophy. As a PARG inhibitor gallotannin treatment also showed protection in PARP cleavage which is a hallmark for apoptotic cell death signifying the protective role of gallotannin in cell death signalling.

Tormentil (no details on the herbal preparation and concentration) showed antioxidant activity in a cell-free oxidant-generating system as well as in sigmoid or rectal mucosal biopsies obtained from patients with active ulcerative colitis (Langmead et al. 2002).

Effect on histamine release

The effects of tannins and related polyphenols on potassium superoxide- and compound 48/80-induced histamine release from rat peritoneal mast cells were examined. Pre-treatment with hydrolysable tannins (1-100 µM) significantly inhibited potassium superoxide-induced histamine release. For example agrimoniin inhibited the potassium superoxide- induced histamine release wirh an IC_{50} of 0.68 µM, the compound 48/80-induced histamine release with an IC_{50} of 0.49 µM. The inhibitory effect on histamine release caused by different stimulants suggested that ellagitannins act as cell membrane stabilizers as well as radical scavengers (Kanoh et al. 2000).

Antitumor effects

Agrimoniin (concentration approximately 1% in the herbal substance) was identified as a potential antitumor agent by Miyamoto et al. (1987). Agrimoniin inhibited almost completely the growth of ascites type and solid type tumours in mice in a dose of 10 mg/kg when applied intra-peritoneally. Murayama et al. (1992) found that agrimoniin induces the interleukin-1 secretion dose-dependently, which was interpreted as possible mechanism for the antitumor activity.

Miyamoto et al. (1988) found that agrimoniin in a dose of 10 mg/kg enhanced *in vitro* the cytotoxic potential of several effector peritoneal exudate cells with different induction kinetics. The earlier response is an enhanced NK cell activity of non-adherent peritoneal exudate cells, later responses were enhanced cytotoxic activity of adherent cells and an antibody-dependent macrophage-mediated cytotoxic activity.

Assessor's comment:
Considering the low amount of agrimoniin in the herbal substance (about 1%) these findings seem to be of minor relevance for the oral and oromucosal use of tormentil.

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

No specific data available.

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

Acute Toxicity:

Dry extract (extraction solvent acetone/water 75:25): in dosages of 300 mg/kg p.o. and 200 mg/kg i.p. no signs of toxicity in mice (Lund & Rimpler 1985).

A dry extract prepared by maceration with water was applied to rats and mice by the intra-gastric route in dosages of 2.5 g/kg and 6.8 g/kg respectively. Further, a single dose was applied intraperitoneally in dosages of 3.8 g/kg in mice and 14.5 g/kg in rats. No signs of toxicity could be observed, the macroscopical and microscopical investigation of the internal organs revealed no pathological changes. The tested doses correspond to several hundreds of grams of extract for a person with 75 kg (Shushunov et al. 2009).

No tests on genotoxicity, carcinogenicity and reproductive toxicity have been performed.

Tannins may have carcinogenic potential; this is for example documented for oak (Labieniec & Gabryelak 2003). It is not clear whether these findings are relevant for tormentil, too.

3.4. Overall conclusions on non-clinical data

The astringent effect of the tannins makes the use of tormentil plausible in the proposed indications. Although the data on toxicology are limited there are no safety concerns for the use as traditional herbal medicinal product.

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

In the study of Huber et al. (2007, see 4.2.1) neither undegraded nor metabolized tannins could be detected by LC-MS in 15 patient sera even after application of 3000 mg/d of an ethanolic dry extract.

No data available regarding other constituents of tormentil.

4.2. Clinical Efficacy

4.2.1. Dose response studies

In an open-label study Huber et al. (2007) investigated the safety, pharmacology and clinical effects of different doses of a commercial ethanolic dry extract (tannin content 15-22%). No further data are available with regard to the extract.

Fifteen patients with active ulcerous colitis finished the study. During treatment with Tormentil extracts, the CAI (Colitis activity index) was reduced from a mean of 8.3 to 3.9 when participants took 2400 mg/d, which was statistically significant. In addition, stool frequency, bloody stool and C-reactive protein decreased. Although the posology was very high, the reported adverse effects were mild (heartburn, stomach discomfort, nausea).

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

Forty children in the age from 3 months to 7 years suffering from rotavirus diarrhoea were included in a clinical trial by Subbotina et al. (2003). The children in the active group received 3 drops tormentil extract per year of life three times daily until discontinuation of the diarrhoea or at maximum for 5 days. The study medication was a tincture (1:10, extraction solvent ethanol 40%). The placebo was an

alcohol extract of Indian teas which were identical in appearance and taste with tormentil tincture. The duration of the diarrhoea was in the treatment group 3 days, in the placebo group 5 days. No side effects were reported.

Assessor's comment:
There is no documented medicinal use of the study medication in the EU. The tincture used in this study is less concentrated compared to the herbal preparations which comply with the requirements on THMPs according to Dir. 2004/24 EC. Additionally, there is no posology for children and adolescents published for any of the herbal preparations included in the monograph.
Therefore the use in children and adolescents cannot be recommended. However, the data support the traditional use of tormentil for the treatment of diarrhoea in adults.

4.3. Overall conclusions on clinical pharmacology and efficacy

The published clinical trials give only preliminary data. They support the traditional use of tormentil. However, the level of evidence does not support well-established use.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

None reported.

5.3. Adverse events and serious adverse events and deaths

The only source of documented adverse effects is the study by Huber et al. (2007). All side effects were mild, although 62% experienced mild gastrointestinal symptoms. One of the 15 patients developed worsening of colitis and was hospitalized.

5.4. Laboratory findings

No specific data available.

5.5. Safety in special populations and situations

No specific data available.

5.6. Overall conclusions on clinical safety

The medicinal use of Tormentillae rhizoma can be regarded as safe.

6. Overall conclusions

Risk – benefit assessment

Since no specific risks are known regarding the oral and oromucosal use of herbal preparations of tormentil, there are no limitations from the herbal preparation when used in adults.

Persistent diarrhoea may cause dehydration and loss of electrolytes. Rehydration and substitution of electrolytes are the primary therapeutic goals. Acute, unspecific diarrhoeas are in most cases self-limiting diseases, a supportive treatment with astringents like tormentil may help to reduce the duration and the severity of the complaints. However, if the symptoms persist for more than 3 days the diarrhoea should be treated and monitored by a doctor.

Only limited data is available regarding the use of tormentil in children and adolescents in the case of diarrhoea. Astringents like purified tannins are recommended in standard literature for children because of their safety compared to therapeutic alternatives (Mutschler et al. 2008). However, acute diarrhoea may be life-threatening especially for young children when not properly treated. Therefore the use of tormentil in the case of diarrhoea in children and adolescents is not suitable for a traditional herbal medicinal product. Moreover, no data on the safe use in children and adolescents are published for the herbal preparations which are included in the monograph. Therefore the use should be restricted to adults.

The use as a gargle in the case of inflammations in the mouth does not show any limitations. However, there are no data regarding a posology in children and adolescents available. Therefore the use should be limited to adults.

No data are available on the safe use during pregnancy and lactation. Therefore the use of tormentil is not recommended during pregnancy and lactation.

Annex

List of references