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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Polygonum aviculare* L., herba Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Polygonum aviculare</i> L., herba
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for decoction preparation for oromucosal use.
Rapporteur(s)	B. Jansone
Peer-reviewer	J. Viguet Poupelloz

Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Polygonum aviculare* 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 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

In accordance with the European Pharmacopoeia (8<sup>th</sup> ed., 07/2013:1885) knotgrass (*Polygoni avicularis* herba) consists of whole or fragmented dried flowering aerial parts of *Polygoni aviculare* L. s.l. The minimum content of flavonoids in dried drug: 0,30%, expressed as hyperoside (C<sub>21</sub>H<sub>20</sub>O<sub>12</sub>; M<sub>r</sub> 464.4) (dried drug).

In other pharmacopoeias and text books *Polygoni avicularis* herba is defined as follows:

- the whole or cut dried flowering aerial parts of *Polygonum aviculare* L. (WHO monographs plants on medicinal plants commonly used in the Newly Independent States [NIS] 2010),
- the dried herb, occasionally containing roots of *Polygonum aviculare* L. gathered during flowering (Blumenthal *et al.* 1998; Österreichisches Arzneibuch 1981),
- whole herb of *Polygonum aviculare* L. (Poradnik Terapeutyczny 1975; Weiss and Fintelman V 2000; Fintelman and Weiss 2006),
- whole herb of *Polygonum aviculare* L. collected during flowering (Produse farmaceutice românești 1970; Pētersone 1961; Rubine *et al.* 1977; Rubine and Īriste, 1999),
- whole herb of *Polygonum aviculare* L., sometimes with the root, collected during the flowering season and dried, as well as the fresh aerial parts collected during the flowering season (Gruenwald *et al.* 2000; 2004; 2007; Wyk and Wink 2005).

### Description and origin of the plant

The *Polygonaceae* family consists of about 800 species and the *Polygonum* genus comprises about 300 species distributed throughout the world - in Europe (31 species), Asia, North Africa, North America and is also introduced into South America. *Polygonum aviculare* L. is native to Europe and Asia (China, Korea etc). In European Union (EU), it is mainly collected in Eastern Europe. It is a sturdy annual herbaceous plant and widely distributed mainly in fields or roadsides (Świątek *et al.* 1986; Karlsson 2000; Sawicka *et al.* 2002; Costea and Tardif 2005, Wyk and Wink 2005 Narasimhulu *et al.* 2014; Styles 1962).

Knotgrass is procumbent and spreads along the ground. The stem is slender (diameter 0.5 – 2 mm), branched, with nodes, cylindrical and longitudinally striated. Average length of the stem is 30 cm. Leaves are small, narrow, sessile and glabrous entire. The characteristic of the plant is the sheath-like stipules (ochrea) which have form of a lacerated membrane in silver and brown colour at the base. Very small flowers have 5 greenish-white perianth segments, the tips of which are often coloured red, generally flowered from June-September. The fruits (2 – 4 mm) are brown to black ovate, triangular nuts, often punctate or striate (European Pharmacopoeia 8<sup>th</sup> ed., 07/2013:1885; Österreichisches Arzneibuch 1981; Wichtl 2004; Wyk and Wink 2005).

*Polygoni avicularis* herba is known under the following other names: knotgrass (English); Vogelknöterichkraut (German); maura sūrene (Latvian); takažolių žolė (Lithuanian); Ziele rdestu ptasiego (Polish); nař rdesna ptačího (Czech); madárkeserűfű virágos hajtás (Hungarian); Stavikrvová vňar (Slovak language); Vejpileurt (Danish); Vogelknöterichkraut (German).

## Constituents

The following constituents of knotgrass (*Polygoni avicularis herba*) according to existing references are reported in the literature:

**Flavonoids** (0.1-1%; rarely 2.5-3%): derivatives of kaempferol, quercetin and myricetin, particularly avicularin (quercetin-3-*O*-arabinoside approximately 0.2%), juglanin (kaempferol-3-*O*-arabinoside), hyperoside, quercitrin, quercetin-3-galactoside, as well as vitexin, isovitexin, rhamnetin-3-*O*-galactoside, rhamnazin hydrogen sulphate, myricetin-3-*O*-fhamnoside, rutin, astragalín, isoquercitrin, miquelianin, spiraeoside, orientin, myricitrin, desmanthin-1, luteolin, betmidin, taxifolin, isorhamnetin, apigenin (Poradnik Terapeutyczny 1975, Granica *et al.* 2013b; Gruenwald *et al.* 2000; 2004; 2007; Haverland 1962; Kim *et al.* 1994; Malinowska 2013; Nugroho *et al.* 2014; Smolarz 2002 (a,b); Wichtl 2004; Wyk and Wink 2005; WHO monographs NIS 2010; Xiuqin and Lishen 1989). Recently some new flavonoids were isolated: liquiritin and cinaroside (Yunuskhodzhaeva and Eshbakova 2010), 5,3'-dihydroxy-4'-*O*-angeloxyflavone-7-*O*- $\beta$ -D-glucopyranoside (Sun *et al.* 2002). Five new flavones were isolated: 5,7- dihydroxy-6-methoxyflavane, 5,7- dihydroxy flavane, 5,7- dimethoxy-4'-hydroxyflavane, morin-7-*O*- $\beta$ -D-glucoside and 5- hydroxyl-3'-methoxyflavanone-7-*O*-rutinoside (Zheng *et al.* 1999). New dimeric procyanidin glucoside: catechin 3-*O*-acetate-(4 $\alpha$ →8)-catechin 3-*O*-acetate-3'-*O*- $\beta$ -D-glucopyranoside was isolated in 2012 (Cong *et al.* 2012).

**Tannins** (3.5- 4%): rhatannin, gallo- and catechol tannins (Gruenwald *et al.* 2000; 2004; 2007; Wyk and Wink 2005; WHO monographs NIS 2010).

**Phenolic carboxylic acids:** caffeic, chlorogenic, gallic and protocatechuic acids (Sawicka *et al.* 2002; Świątek *et al.* 1986; Wichtl 2004; WHO monographs NIS 2010).

**Naphthoquinone:** 6-methoxyplumbagin (Al-Hazimi and Haque 2002).

**Hydroxycoumarins:** umbelliferone, scopoletin (Gruenwald *et al.* 2000; 2004; 2007).

**Lignans:** lignin glycoside, aviculin (Gruenwald *et al.* 2000; 2004; 2007; WHO monographs NIS 2010).

**Sterols:** mainly  $\beta$ -sitosterol (Narasimhulu *et al.* 2014).

**Saponins:** triterpenoid saponins, mostly oleanolic acid (Narasimhulu *et al.* 2014).

**Anthraquinones:** emodin (Cai *et al.* 2004).

**Silicic, tartaric and formic acids** (1%): present as water-soluble silicates (Poradnik Terapeutyczny 1975; Gruenwald *et al.* 2000; 2004; 2007; WHO monographs NIS 2010).

**Carbohydrates:** glucose, galactose, arabinose, sucrose, rhamnose, galacturonic acid (Yakovlev *et al.* 1985; WHO monographs NIS 2010).

**Other constituents:** essential oils, carotene, vitamins C and K, (Petersone 1961; Rubine *et al.* 1977; Yunuskhodzhaeva and Eshbakova 2010; Yunuskhodzhaeva and Abdullabekova VH 2012).

- Herbal preparation(s)

Comminuted herbal substance

- 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.

Knotgrass is also available as a component of combination medicinal products with many other herbal substances/herbal preparations (for instance: *Foeniculi fructus*, *Myrtilli herba*, *Galegae herba*, *Rubi fruticosi folium*, *Salviae officinalis folium and herba*, *Taraxaci radix cum herba*, *Urticae herba* etc).

The following combination medicinal herbal products containing *Polygoni avicularis herba* are currently registered/marketed and available on the EU market. This information was provided by the National Competent Authorities in the overview of the marketed products:

- Czech Republic: herbal teas with 8-9 substances.
- Germany: herbal tea with 8 substances.
- Hungary: combination product with 4 substances.
- Latvia: paste for oral use with 9 substances.
- Poland: paste for oral use with 10 substances and combination product for bath preparation with 6 substances.
- Slovak Republic: combination product with 10 substances.
- Austria, Denmark, Latvia and United Kingdom: combination product in a form of tablet or capsules with more than 20 substances.

This assessment report and the European Union herbal monograph refer exclusively to *Polygoni avicularis herba* as a single ingredient. The European Union herbal monograph describes the use of the comminuted herbal substance for tea preparations and for preparation of decoction for oromucosal or oral use

Vitamin(s): not applicable

Mineral(s): not applicable

## **1.2. Search and assessment methodology**

Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations, electronic databases and other sources were used to assess information available on traditional use, pharmaceutical, non-clinical, clinical data and current indications on *Polygoni avicularis herba*.

Search engines used: Google, Google Scholar; key words: *Polygonum aviculare L.*, *Polygoni avicularis herba*, *knotgrass*, *Vogelknöterichkraut*

Scientific databases: PubMed, ScienceDirect, Scopus, Scifinder, Web of Science, EMBASE, EBSCO, Dawsonera; search period 1.06.2014-1.03.2015; key words: *Polygonum aviculare L.*, *Polygoni avicularis herba*, *knotgrass*, *Vogelknöterichkraut*

Medical databases: UpToDate, Cochrane library, PubMed; search period 1.06.2014-1.03.2015; key words: *Polygonum aviculare L.*, *Polygoni avicularis herba*, *knotgrass*, *Vogelknöterichkraut*

Toxicological databases: Toxnet; search period 1.06.2014-1.03.2015; key words: *Polygonum aviculare L.*, *Polygoni avicularis herba*, *knotgrass*, *Vogelknöterichkraut*

Other resources:

- Libraries: hand searches in handbooks, textbooks and Pharmacopoeias on *Polygoni avicularis* herba and knotgrass at the various libraries were performed, namely, EMA, University of Latvia, Rigas Stradinu University, The State Agency of Medicines of Latvia, Central library in Riga.
- Other databases: The World Health Organization, National Centre for Complementary and Alternative Medicine (NCCAM), The division for Complementary and Alternative Medicines of the Federal Institute for Drugs and Medical Devices (BfArM)

References in Latvian, English, German, Polish and Russian were assessed. Only references found to be relevant for assessment are included in the list of references.

## **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**

According to the information provided by the National Competent Authorities in the overview of the marketed products, monocomponent medicinal products containing *Polygonum aviculare* L., herba are available in markets of Lithuania and Poland.

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
<p><i>Polygoni avicularis</i> herba; comminuted herbal substance</p>	<p>a) Traditionally used in mild urinary tract inflammation</p> <p>b) Traditionally used in mild inflammation of the mouth and throat.</p>	<p>Comminuted herbal substance <i>Adolescents, adults and elderly</i></p> <p>a) Single dose: decoction of 3 g of herbal substance in 200 ml for oral use 2 times daily between meals</p> <p>Method of administration: oral use</p> <p>Duration: 2 weeks</p> <p>b) Single dose: 3g (2 teaspoons) in glass of water (200-250ml) as freshly prepared decoction for rinsing or gargling between meals 2 times a day.</p> <p>Method of administration: oromucosal use</p> <p>Duration: 1 week</p>	<p><b>Poland</b> TUR since 19.05.2013.</p>
<p><i>Polygonum aviculare</i> L., herba; comminuted herbal substance for tea preparation</p>	<p>Traditional herbal medicinal product used for the relief of symptoms of common cold.</p>	<p>Comminuted herbal substance for tea preparation. <i>Adolescents, Adults and Elderly</i></p> <p>Single dose Herbal tea: 1,5-2 g of the comminuted herbal substance ad to 150 ml cold water, then bring to boil. As a herbal infusion use 3–4 times daily, 30 min. before meal. Daily dose: 5-8 g <i>Duration of use</i> 1 week.</p>	<p><b>Lithuania</b> TUR since 05.07.1994</p>

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

Combination products containing *Polygonum aviculare* L., herba with few as well as up to 20 other herbal substances/herbal preparations (for instance: *Salviae officinalis* herba, *Thymi* herba, *Taraxaci* radix cum herba etc) are available in Austria, Czech Republic, Denmark, Germany, Hungary, Latvia, Poland, Slovak Republic, United Kingdom. For more detailed description see below.

Czech Republic:

a)

*Pharmaceutical form:* Herbal tea containing (in 1 tea bag): 170 mg *Phaseoli* fructus sine semine, 150 mg *Myrtilli* herba, 150 mg *Salviae officinalis* herba, 120 mg *Galegae* herba, 100 mg *Polygoni avicularis* herba, 80 mg *Taraxaci* radix cum herba, 80 mg *Rubi fruticosi* folium, 80 mg *Foeniculi* fructus, 20 mg *Bardanae* radix.

*Indication:* an adjuvant in diabetes

*Posology:* 1 tea bag /250 ml of boiling water 3 times daily

On the market since 1969

b)

*Pharmaceutical form:* Herbal tea containing (in 1 tea bag): 225 mg *Salviae officinalis* folium, 225 mg *Althaeae* radix, 225 mg *Polygoni avicularis* herba, 225 mg *Thymi* herba, 225 mg *Urticae* herba, 150 mg *Foeniculi* fructus, 75 mg *Sambuci* flos, 75 mg *Plantaginis* folium, 75 mg *Liquiritiae* radix.

*Indication:* an adjuvant for treatment of acute and chronic upper respiratory tract catarrhs.

*Posology:* 1 tea bag /250 ml of boiling water 3 times daily.

On the market since 1971.

c)

*Pharmaceutical form:* Herbal tea containing (in 1 tea bag): 413 mg *Betulae* folium, 337 mg *Uvae ursi* folium, 150 mg *Ononidis* radix, 150 mg *Petroselinii* radix, 165 mg *Polygoni avicularis* herba, 150 mg *Urticae* herba, 105 mg *Millefolii* herba, 30 mg *Sambuci* flos.

*Indication:* an adjuvant for treatment of symptoms of mild lower urinary tract infections such as burning sensation during urination and frequent urination.

*Posology:* 1 tea bag /250 ml of boiling water 3-5 times daily.

On the market since 1969.

Germany:

*Pharmaceutical form:* herbal tea containing (in 1 sachet (1.6 g)): 240 mg *Foeniculi amari* fructus, 208 mg *Thymi* herba, 192 mg *Tiliae* flos, 192 mg *Polygoni avicularis* herba, 176 mg *Lichen islandicus*, 96 mg *Primulae* flos, 64 mg *Lamium album* flos, 64 mg *Verbascum thapsus* flos.

*Indication:* Traditional herbal medicinal product to liquefy mucus. (Traditionell angewendet zur Unterstützung der Schleimlösung im Bereich der Atemwege).

*Posology:* 4-6 times daily 1 cup of tea (1 sachet/cup).

On the market since: at least 1978.

Hungary:

Combination product containing: 450 mg *Graminis* rhizoma *pulv.*, 375 mg *Agrimoniae* herba *pulv.*, 375 mg *Taraxaci* radix *pulv.*, 225 mg *Polygoni avicularis* herba *pulv.* /filter(1.5g).

*Recommended:* to promote the elimination of excretas from the body.

Latvia:

Pharmaceutical form: Oral paste.

100 g of paste contains 67,2 g of composed extract: *Extractum hydroalcoholicum compositum* (1:1,3-1,6) ex: *Petroselinum sativum* Hoffm., radix; *Trigonella foenum - graecum* L., semen; *Polygonum aviculare* L., herba; *Agropyron repens* (L.) Beauv., rhizoma; *Betula pendula* Roth or/and *Betula pubescens* Ehrh., folium; *Equisetum arvense* L., herba; *Levisticum officinale* Koch., radix; *Solidago virgaurea* L., herba; *Allium cepa* L., squama (7/6/6/5/4/4/4/2/2).

Indication: in cases of infections of urinary tract, kidney and bladder, for treatment and prevention of nephrolithiasis.

Posology: Adults 3 - 4 times daily teaspoon (approximately 5 g) paste, dissolved in 1/2 cup of warm boiled water.

On the market since 2000.

Poland:

a)

Pharmaceutical form: Oral paste containing in 100 g of products 67,2 g of composed extract: *Extractum compositum* (1:1,3-1,6) ex: 12,5 parts *Agropyri rhizomate*, 5,0 parts *Allii cepae squamata*, 10,0 parts *Betulae folio*, 15,0 parts *Foenugraeci semine*, 17,5 parts *Petroselini radice*, 5,0 parts *Solidaginis herba*, 10,0 parts *Equiseti herba*, 10,0 parts *Levistici radice*, 15,0 parts *Polygoni avicularis herba*.

Indication: Traditional herbal medicinal product used adjunctively in infections and inflammatory conditions of the urinary tract, urolithiasis (in fine streaks, the so-called kidney gravel) and prophylactically nephrolithiasis.

Posology: Adults 3 - 4 times daily teaspoon (approximately 5 g) paste, dissolved in 1/4 cup of warm boiled water.

On the market since 06/01/1961.

b)

Pharmaceutical form: Herbal mixture for preparation a bath containing: 25,0 g *Quercus cortex*, 20,0 g *Matricariae flos*, 17,5 g *Polygoni avicularis herba*, 17,5 g *Salviae folium*, 17,5 g *Urticae folium*, 2,5 g *Calendulae flos*

Indication: Traditional herbal medicinal product used to wash of the area of external female genital organs in mild inflammation states.

Posology: 15-20 g of herbal mixture (6 spoons) pour with 1,5 l of hot water, boil 10 minutes in covered vessel, let stand 15 minutes, strain. Used for washing.

On the market since 1956.

Slovak Republic:

Contain: *Polygoni avicularis herba*, *Phaseoli fructus s.sem*, *Myrtilli herba*, *Salviae herba*, *Galegae herba*, *Taraxaci radix c.herba*, *Rubi fruticosi folium*, *Foeniculi fructus*, *Bardanae radix*, *Liquiritiae radix*.

Austria, Denmark, Latvia and United Kingdom:

Combination medicinal product containing *Polygoni avicularis herba* together with more than 20 active substances in a form of tablet or capsules is available on these markets.

Indications mentioned: a traditional herbal medicinal product used to relieve the symptoms of Raynaud's syndrome and for the relief of symptoms associated with minor venous circulatory disturbances, such as tired heavy legs, pain, swelling, and for calf cramps; herbal medicinal product for

the relief of walking provoked pains in the legs due to insufficient blood circulation (claudicatio intermittens).

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

Czech Republic:

The herbal substance and preparations thereof are available on the market as food supplements as well.

Italy:

*Polygoni avicularis herba* is included in the list of herbal substances and herbal preparations allowed in food supplements, published on the website of the Italian Ministry of Health, with the following indication: 'Regulation of intestinal transit; Counteraction of disturbances of menstrual cycle; Functionality of digestive system; Functionality of upper airways.'

Latvia:

The herbal substance and preparations thereof are available on the market as food supplements (mono and combination products).

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

Not applicable.

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

The herbal substance knotgrass (*Polygoni avicularis herba*) is included in many handbooks, compendia, monograph such as Hagers Handbuch (Frerichs *et al.*, 1927), Lehrbuch der Biologischen Heilmittel (Madaus, 1938, 1976), Drogenkunde (Hoppe, 1942), Farmakopea Polska (1970), Gift- and Arzneipflanzen von Mitteleuropa (Gessner and Orzechowski, 1974), Braun H (1974), Poradnik Terapeutyczny (1975), Hagers Handbuch (List & Hörhammer, 1977), Teedrogen (Wichtl, 1984), Kommission E Monographie, 1987, The Complete German Commission E Monographs (Blumenthal *et al.*, 1998), Herbal drugs and Phytopharmaceuticals (Wichtl, 2004), Rational Phytotherapy (Schulz *et al.*, 2004), PDR for Herbal medicines (Gruenwald *et al.*, 2004 and 2007), Medicinal plants of the world (Wyk and Wink, 2005), A Compendium 'Medicinal Herbs' (Gehrmann *et al.*, 2005), Herbal Medicine (Weiss and Fintelmann, 2000), Lehrbuch der Phytotherapie (Fintelmann and Weiss, 2006), WHO Monographs on medicinal plants commonly used in the newly independent states (WHO monographs NIS 2010), in the list of herbals used by herbal industry in Poland (Ożarowski, 1978) and mentioned in the ordinance of the Minister of Health of Poland (Rozporządzenie Ministra Opieki Społecznej. Poz 454., 1938).

The herbal substance knotgrass is mentioned in well-known handbooks as an expectorant and secretolytic to treat cough, bronchial catarrh and is also recommended for use in inflammation of the mouth and upper respiratory tract (Hagers Handbuch (Frerichs *et al.*, 1927), Madaus, 1938 and 1976; Braun, 1974; Poradnik Terapeutyczny, 1975; Wichtl, 1984; Kommission E Monographie, 1987; Blumenthal *et al.*, 1998; Weiss and Fintelmann, 2000; Wichtl, 2004; Gruenwald *et al.*, 2000, 2004 and 2007; Gehrmann *et al.*, 2005; Wyk and Wink, 2005). Several monographs and handbooks described the usage of knotgrass for the treatment of urinary tract infection with difficult painful urination, kidney stones and gallstone, gout and diuretic effect (Madaus, 1938 and 1976; Hoppe, 1942; Haverland,

Roeske, 1955; 1962; Poradnik Terapeutyczny, 1975; Ożarowskiego, 1976, Wichtl, 1984; Mashkovsky, 1985 and 1993; Pētersone, 1961; Rubine *et al.* 1977; Skutelis and Pakalns, 2005 Sokolov and Zamotaev, 1984).

Diuretic activity of *Polygoni avicularis herba* was described also in the Pharmacopoeia of the former Soviet Union (Mashkovsky, 1985). In Lithuania before 1990 *Polygoni avicularis herba* was available as medicinal product with indication for the treatment of urinary tract disorders. Also in Latvia from 1999 till 2006 *Polygoni avicularis herba* containing medicinal product was used to increase the amount of urine to achieve flushing of the urinary tract and in case of kidney stones. In Poland knotgrass has been traditionally used as diuretic with evidence in the literature going back at least to the middle of the last century (Roeske, 1955; Farmakopea Polska, 1970; Poradnik Terapeutyczny, 1975; Ożarowskiego, 1976; Ożarowski, 1978) and currently one medicinal product as single ingredient herbal tea is available on the Polish market for the treatment of mild urinary tract inflammation.

In Madaus (1938, 1976) a broad spectrum of traditional usage is listed, for example, in bleedings (uterus, stomach, intestine, lung); diseases of the gastro-intestinal tract (ulcus ventriculi et duodeni, diarrhoea, gastroenteritis); catarrh of the lungs, tuberculosis, irritating cough, asthma, hoarseness; diseases of kidney and bladder, kidney stones and gravel.

Usage based on tradition in folk medicine indicated the external usage of the knotgrass for skin disorders such as eczema and vulval itching, skin wounds and ulcers as well as internally used in articular pain, rheumatism, as hemostatic in cases of haemorrhage and in cholelithiasis (Gruenwald *et al.*, 2000, 2004 and 2007; Hoppe, 1942; Muszyński, 1954; Rubine *et al.*, 1977; List & Hörhammer, 1977; Turowa *et al.* 1987; Wichtl, 1984; Rios *et al.* 1987; Novaretti and Lemordant 1990; Wichtl, 2004; Wyk and Wink, 2005).

Chinese phonetic name for knotgrass is Bian Xu. In China knotgrass has been used in traditional medicine since ancient times as diuretic, for throat and bronchial ailments as well as to treat skin problems (Gruenwald *et al.*, 2000, 2004 and 2007; WHO monographs NIS 2010). Other usages in Chinese medicine are mentioned for gonorrhoea, jaundice, tapeworm in children (Gruenwald *et al.*, 2000, 2004 and 2007).

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Comminuted herbal substance or equivalent preparations	<ul style="list-style-type: none"> <li>- Mild catarrhs of the respiratory tract,</li> <li>- Inflammatory changes to the oral and pharyngeal mucosa</li> </ul>	Daily dosage: 4-6 g as herbal tea and other galenical preparations for internal use and local application	Blumenthal <i>et al.</i> , 1998
Comminuted herbal substance or equivalent preparations	<ul style="list-style-type: none"> <li>- Cough and bronchial catarrh,</li> <li>- Inflammation of the mouth and upper respiratory tract</li> </ul>	Single dose: 1.5 g to be taken 3-5 times daily	Wyk and Wink, 2005
Comminuted herbal substance or equivalent preparations	<ul style="list-style-type: none"> <li>- Mild catarrhs of the respiratory tract,</li> <li>- Inflammatory changes to the oral and pharyngeal mucosa.</li> </ul>	Single dose: 1.5 g as infusion and other galenical preparations for internal use and local application taken 3-5 times daily  Daily dosage: 4-6 g	Wichtl, 2004
Comminuted herbal	- Cough/bronchitis,	Single dose: 1.5 g as	Gruenwald <i>et al.</i> , 2000,

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
substance or equivalent preparations	- Inflammations of the mouth and pharynx	infusion and other galenical preparations for internal use taken 3-5 times daily Daily dosage: 4-6 g  Infusion for external use: daily dose of 5 g for local application	2004 and 2007
Comminuted herbal substance or equivalent preparations	- Catarrhs of the respiratory tract, - Inflammatory of mouth, throat and pharyngeal mucosa.	Single dose: 1.5 g/150mL as cold maceration for internal and local (gargle and cleansing) use, 3-5 times daily  Daily dosage: 4-6 g  <i>Duration of use:</i> if the acute symptoms persist longer than 1 week or illness is recurring, a medical practitioner should be consulted	Gehrmann <i>et al.</i> , 2005
Comminuted herbal substance or equivalent preparations	- For treatment of gingivitis, - For the relief of cough and cold symptoms,	Single dose: 1.5 g as infusion for oral use taken 3-5 times daily  Daily dosage: 4 - 6 g	WHO monographs NIS 2010
Comminuted herbal substance or equivalent preparations	- Catarrh of the respiratory tract - Inflammatory changes to the oral mucosal membrane	No information	Weiss and Fintelmann, 2000
Comminuted herbal substance or equivalent preparations	as adjuvant in coughs and bronchial catarrh; astringent gargle for the symptomatic treatment in the mouth and throat	Single dose: 1.5 g as decoction use 3-5 times daily	Wichtl, 1984
Comminuted herbal substance	For the treatment of urinary tract disorders	Single dose: 2 g in glass of water for oral use as decoction, 2-3 times daily	Ożarowski, 1978;
Comminuted herbal substance or equivalent preparations	As diuretic, In gout, bad metabolism, pulmonary diseases	About 5 – 10 g in glass of water for oral use, taken ¼ -1/2 of the glass 2-3 times daily	Poradnik Terapeutyczny, 1975
Comminuted herbal substance	As diuretic, bad metabolism, as astringent	Single dose: 10-20 g in 2 glasses of water (400-500 ml) for oral use as decoction, 3 times daily	Ożarowskiego, 1976
Comminuted herbal substance	As an adjuvant pulmonary therapy, astringent gargle for the symptomatic treatment in the mouth and throat, in gout, diuretic	1,5 g in about 150 ml water as infusion or decoction Daily dosage: 4,8 - 7,2 g	<u>Hagers Handbuch (List &amp; Hörhammer, 1977).</u>
Comminuted herbal substance	- catarrh of the bladder, - cough, - kidney stones and gallstone,	Infusion for oral use of 20 g of herbal substance in 200 ml, take 1 tablespoon 3 times daily	Rubine <i>et al.</i> 1977

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Comminuted herbal substance	- cough and bronchial catarrh, - gout - as diuretic	1 tablespoon 3 times daily	Pētersone, 1961
Comminuted herbal substance	As diuretic	No information	Haverland, 1962
Comminuted herbal substance	As diuretic in nephrolithiasis	Daily dosage: 2 glasses (400 - 500ml) of 10% Infusion, usage divided in several portions	Roeske, 1955
Comminuted herbal substance	As adjuvant therapy in the lung disorders, for gout as diuretic	No information	Hoppe, 1942
Comminuted herbal substance	- Catarrh of the lungs, irritating cough, - diseases of kidney and bladder, kidney stones and grave - in bleedings, - gastro-intestinal tract disorders	Daily dosage: 4,8-7,2 g (2-3 teaspoons) as infusion	Madaus, 1938, 1976
Comminuted herbal substance	- throat and bronchial catarrh	No information	<u>Hagers Handbuch</u> (Frerichs <i>et al.</i> , 1927)

### 2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance for tea preparation	For the relief of symptoms of common cold	<i>Adolescents, Adults and Elderly</i> Single dose Herbal tea: 1,5-2 g of the comminuted herbal substance in 150 ml of water 30 min before meal  3-4 times daily  Daily dosage: 4,5 - 8 g  Method of administration: oral use  Duration of use: 1 week	TUR use in Lithuania since 05.07.1994  Posology data from literature since 1938. Madaus, 1938, 1976; Pētersone, 1961; Poradnik Terapeutyczny, 1975; <u>Hagers Handbuch (List &amp; Hörhammer, 1977;</u> Wichtl, 1984; Blumenthal <i>et al.</i> , 1998; WHO monographs NIS 2010; Gruenwald <i>et al.</i> , 2000, 2004 and 2007; Wichtl, 2004; Wyk and Wink, 2005; Gehrman <i>et al.</i> , 2005.

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance	Mild inflammation of the mouth and throat	Single dose: 3g (2 teaspoons) in glass of water (200-250ml) as freshly prepared decoction for rinsing or gargling between meals 2 times a day.  Method of administration: oromucosal use  Duration: 1 week	TUR use in Poland since 19.05.2013.  Posology data from literature since 1975. Poradnik Terapeutyczny, 1975; <u>Hagers Handbuch (List &amp; Hörhammer, 1977)</u> ; Wichtl, 1984; Blumenthal <i>et al.</i> , 1998; Gruenwald <i>et al.</i> , 2000, 2004 and 2007; Wichtl, 2004; Wyk and Wink, 2005; Gehrman <i>et al.</i> , 2005.
Comminuted herbal substance	Mild urinary tract inflammation	Adults Single dose: decoction of 3 g of herbal substance in 200 ml for oral use 2 times daily, between meals.  Daily dose: 6 g  Method of administration: oral use  Duration: 2 weeks	TUR use in Poland since 19.05.2013.  Posology data from literature since 1938. Madaus, 1938, 1976; Petersone, 1961; Poradnik Terapeutyczny, 1975; Ożarowskiego, 1976; <u>Hagers Handbuch (List &amp; Hörhammer, 1977)</u> ; Rubine <i>et al.</i> 1977; Ożarowski, 1978; Wyk and Wink, 2005.

The most frequently cited indications that can be based on the traditional medicinal use of *Polygoni avicularis herba* refers to the mild catarrhs of the respiratory tract, inflammation of the mouth and upper respiratory tract and renal elimination of water. For those indications the traditional use of *Polygoni avicularis herba* for more than 30 years in European Union in the forms of infusion and decoction is supported by the literature as well as by the medicinal products of *Polygonum aviculare L.*, herba that are available in Lithuania and Poland.

The wording 'traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints' for the therapeutic indication of *Polygoni avicularis herba* related to the urinary tract disorder is formulated in accordance with other approved European Union monographs for traditional herbal medicinal products which have similar properties on urinary tract (eg. *Equisetum arvense L.*, herba) and therefore the use of the standard formulation in the monograph is preferred.

There are no posology specified in the literature and preparations available on the EU market for the topical usage of *Polygoni avicularis herba* for skin disorders therefore this indication is not proposed in monograph. Other indications (eg. in bleedings of the uterus, stomach, intestine, lung) of *Polygoni avicularis herba* mentioned in older books are not acceptable for the herbal medicinal product. On a base of available data, the requirements for the traditional medicinal use according to Directive 2001/83/EC is fulfilled and the European Union Monograph on traditional herbal medicinal product of *Polygoni avicularis herba* can be accepted for the following indications:

#### Indication 1:

For symptomatic treatment of minor inflammations in the mouth or the throat

*In adolescents, adults and elderly:*

Single dose: 1,5 g; rinsing or gargling between meals, 4 - 5 times daily.

Duration of use: 1 week.

#### Indication 2:

For the relief of symptoms of common cold

*In adolescents, adults and elderly:*

Single dose: 1,5 - 2 g; 3 - 4 times daily.

Duration of use: 1 week.

#### Indication 3:

To increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints

*In adolescents, adults and elderly:*

Single dose: 3 g; 2 times daily.

Duration of use: 2 weeks.

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

### 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**

###### **Anti-inflammatory activity**

In vitro studies

###### Aqueous extracts:

Inhibitory effect on prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis of *Polygoni avicularis* herba was studied among other 52 plants of Swedish traditional medicine used to treat inflammatory diseases and/or wounds (Tunón *et al.*, 1995). The dried plant material was extracted twice with water (1:20 and 1:10) for 48h at room temperature and then lyophilized. The extract of *Polygoni avicularis* herba induced high (83 %) inhibition level on platelet activating factor (PAF)-induced exocytosis and moderate (52 %) inhibition effect on prostaglandin biosynthesis indicating an anti-inflammatory activity of this herbal substance (Tunón *et al.*, 1995).

###### Isolated constituents:

Inhibition of elastase release of 11 flavonol glucuronides (myricetin 3-O- $\beta$ -D-glucuronide, mearsetin 3-O- $\beta$ -D-glucuronide, quercetin 3-O- $\beta$ -D-glucuronide, isorhamnetin 3-O- $\beta$ -D-glucuronide, kaempferide 3-O- $\beta$ -D-glucuronide, kaempferol 3-O- $\beta$ -D-glucuronide, kaempferol 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide), isorhamnetin 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide), quercetin 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide), quercetin 3-O- $\beta$ -(3''-O-acetyl- $\beta$ -D-glucuronide), kaempferol 3-O- $\beta$ -(3''-O-acetyl- $\beta$ -D-glucuronide)) isolated from *Polygonum aviculare* L. was studied using the model of elastase release inhibition in human neutrophils (Granica *et al.*, 2013a). The *Polygonum aviculare* L. herba (1000 g)



was powdered and extracted with solvents of rising polarity (petroleum ether, chloroform (CHCl<sub>3</sub>), ethyl acetate (AcOEt), acetone (Me<sub>2</sub>CO) and water (H<sub>2</sub>O)). All compounds with exception of kaempferol 3-O-β-D-glucuronide and quercetin 3-O-β-(2"-O-acetyl- β-D-glucuronide) at 1 μM concentration significantly decreased the release of elastase by neutrophils. Myricetin 3-O-β-D-glucuronide, mearsetin 3-O-β-D-glucuronide, quercetin 3-O-β-D-glucuronide and quercetin 3-O-β-(3"-O-acetyl- β-D-glucuronide) exerted similar inhibitory capability as quercetin (served as a control). The obtained data demonstrated the anti-inflammatory activity of *Polygoni avicularis* herba (Granica *et al.*, 2013a).

## Antibacterial activity

### Aqueous extracts:

The pressure-assisted water extraction (PAWE) of *Polygonum aviculare* L. herba was tested for antibacterial activity against *Salmonella Typhimurin*. The results shown that the MIC<sub>99</sub> (the minimum inhibitory concentration) value was significantly decreased to 9.04 (Gou *et al.*, 2011).

### Aqueous and other extracts:

Organic and aqueous solvent extracts (the yield of powder was 41% wt/wt from water extracts, 27% wt/wt from acetone, 17% wt/wt from ethanol and 15% wt/wt from chloroform extracts for the stem, the respective values of 32%, 30%, 20% and 18% wt/wt were obtained for the leaves) of *Polygonum aviculare* herba were evaluated for antimicrobial activities on gram-negative bacteria (*Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *S. paratyphi* and *Shigella flexneri*) and gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, and *Streptococcus pyogenes*) by the paper disc diffusion method using cotrimoxazole and chloramphenicol as standard antimicrobials for comparison of the plant effect. Extracts were used in various concentrations: 0.5 ml of 20.0, 18.0, 15.0, 10.0, 8.0, 5.0, 1.0, 0.5, 0.05 and 0.005 mg/ml. As well as a different concentrations of isolated panicudine dissolved in chloroform (400, 40, 4, 0.4 mg/g) were tested for antimicrobial activity by measurement of inhibition zone (Salama and Marraiki, 2010). The data show that the highest average activity of four plant extracts against the tested organisms had chloroform (e.g. diameter of inhibition zone 28 mm against *Proteus mirabilis*) followed by water extracts (e.g. diameter of inhibition zone 25 mm against *Bacillus subtilis*), ethanol extracts (e.g. diameter of inhibition zone 23 mm against *Salmonella typhi* and *Proteus mirabilis*) and finally the lowest activity was demonstrated by the acetone extracts (diameter of inhibition zone 2 mm against *S. aureus*). The results revealed that all of the plant extracts were effective against most of the tested microorganisms but the leaf extracts generally had lower activity against the test bacteria compared to the stem extracts. Antimicrobial activity of the extracts was unaffected after exposure to heat, but was reduced at alkaline pH. Panicudine expressed very good antimicrobial activity against all Gram-negative and Gram-positive bacteria tested bacteria. In generally low minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of chloroform extracts of *Polygonum aviculare* herba indicated good efficacy towards tested bacteria. The lowest MIC and the MBC were demonstrated against *Salmonella paratyphi*, *Bacillus subtilis* and *Salmonella typhi*. The only exception was higher MIC and MBC values obtained with *Staphylococcus aureus* (Salama and Marraiki, 2010).

*Polygonum aviculare* herba extracted with 95% v/v ethanol. As dried plant extracts were prepared three different concentrations (1.00, 0.10 and 0.01 mg/mL) for the testing against gram-negative (*Acinetobacter baumannii* and *Pseudomonas aeruginosa* from MEDINA's Culture Collection) and gram-positive bacteria (*Staphylococcus aureus*). The extract was considered to show anti-bacterial activity if its percentage of inhibition was more than 60%. Results of this study indicated that *Polygonum aviculare* herba exhibited anti-bacterial activity: inhibition of *Acinetobacter baumannii* was 81±3% for the dose 1.00 mg/mL and inhibition of *Pseudomonas aeruginosa* was 74±6% also for the higher dose

1.00 mg/mL. Gram-positive bacteria (*Staphylococcus aureus*) was inhibited 100±0% by *Polygonum aviculare* herba at the dose of 1.00 mg/mL (Zhang *et al.*, 2013).

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

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
comparable/similar preparations to preparations of the monograph				
Aqueous extracts of <i>Polygonum aviculare</i> L. herba	Concentrations of 0-500 mg/mL	<i>In vitro</i> : extracted with the pressure-assisted water extraction (PAWE) technique, a) assessed measuring of minimum of inhibitory concentration against <i>Salmonella Typhimurium</i>	Gou <i>et al.</i> , 2011	antibacterial activity produced
Aqueous extracts of <i>Polygonum aviculare</i> L. herba	1-0.2 mg/ml	<i>In vitro</i> : evaluation of the inhibitory effect on prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis	Tunón <i>et al.</i> , 1995	anti-inflammatory activity demonstrated
other preparations				
Aqueous-acetone, ethanolic, chloroform extract of <i>Polygonum aviculare</i> L. herba	concentrations of the extracts: 20.0, 18.0, 15.0, 10.0, 8.0, 5.0, 1.0, 0.5, 0.05 and 0.005 mg/ml	<i>In vitro</i> : low minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) was estimated by the paper disc diffusion method	Salama and Marraiki, 2010	antibacterial activity against gram-negative and gram-positive bacteria demonstrated with highest average activity of four plant extracts against the tested organisms had chloroform (e.g. diameter of inhibition zone 28 mm against <i>Proteus mirabilis</i> ) followed by water extracts (e.g. diameter of inhibition zone 25 mm against <i>Bacillus subtilis</i> )
Ethanolic extract of <i>Polygonum aviculare</i> L. herba	1.00, 0.10 and 0.01 mg/mL	<i>In vitro</i> : if its percentage of inhibition of gram-negative ( <i>Acinetobacter baumannii</i> and <i>Pseudomonas aeruginosa</i> from MEDINA's Culture Collection) and gram-positive bacteria ( <i>Staphylococcus aureus</i> ) was more than 60% anti-bacterial activity	Zhang <i>et al.</i> , 2013	anti-bacterial activity was exhibited at the higher dose (1.00 mg/mL) tested: inhibition of <i>Acinetobacter baumannii</i> was 81±3% and for the <i>Pseudomonas aeruginosa</i> was 74±6%. Gram-positive bacteria ( <i>Staphylococcus aureus</i> ) were inhibited 100±0%.

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
		was considered as significant		
single substances				
11 flavonol glucuronides of <i>Polygonum aviculare</i> L. herba, extraction solvent: petroleum ether, chloroform, ethyl acetate, acetone and water	0.5, 1 and 10 µM	<i>In vitro</i> : influence of the release of elastase by neutrophils	Granica <i>et al.</i> 2013a	anti-inflammatory activity demonstrated
paniculine isolated from <i>Polygonum aviculare</i> L. herba extract, extraction chloroform	0.4, 4, 40, 400, mg/g	<i>In vitro</i> : measurement of inhibition zone was estimated	Salama and Marraiki, 2010	antibacterial activity against both gram-negative and gram-positive bacteria demonstrated

### 3.1.2. Secondary pharmacodynamics

#### Antioxidative effects

In vitro:

#### Ethanol extracts:

The free radical scavenging activity of extract powder was determined using free radical scavenging, lipid peroxidation, superoxide radical scavenging assays and hydroxyl radical-induced DNA strand scission assays. In the Hsu (2006) study the *Polygonum aviculare* L. herba powder was extracted in 50% ethanol solution and then was lyophilized and the resulting powder extract was used in the experiments. 1 mg of this extract powder was dissolved in 1 ml of 50% ethanol solution to obtain 1000 µg/ml sample solution. 1000 µg/ml solutions were diluted into series of 1 µg/ml, 5 µg/ml, 10 µg/ml, 20 µg/ml, 50 µg/ml, 100 µg/ml, 200 µg/ml, 500 µg/ml, and 1000 µg/ml with 50% ethanol. Well-known antioxidant compounds such as 1,1-Diphenyl-2-picrylhydrazyl (DPPH) assay, (+)-catechin and L-ascorbic acid were used as controls. The results show that the IC<sub>50</sub> (the concentration required to inhibit radical formation by 50%) value of *Polygonum aviculare* L. extract in free radical scavenging assays is 50 µg/ml, while the IC<sub>50</sub> values of (+)-catechin and ascorbic acid were 35 µg/ml and 50 µg/ml, respectively, indicating that all have inhibitory effect on the DPPH radical. The IC<sub>50</sub> value in superoxide radical scavenging assays for *Polygonum aviculare* L. extract was 0.8 µg/ml but for (+)-catechin it was 40 µg/ml. Most of superoxide radicals were inhibited by 10 µg/ml *Polygonum aviculare* L. extract indicating that the superoxide scavenging activity of *Polygonum aviculare* L. extract is higher than that of (+)-catechin. The data obtained from the lipid peroxidation suppressing activity measured by TBA (2-thiobarbituric acid) assay shown that the IC<sub>50</sub> value of *Polygonum aviculare* L. extract was 16 µg/ml exhibiting similar curve effect of antioxidant activity to (+)-catechin (IC<sub>50</sub> value 17 µg/ml). The results of hydroxyl radical-induced DNA strand scission assay had shown the DNA protective effect of *Polygonum aviculare* L. extract. The total phenolics and flavonoid content of extract were 677.4 ± 62.7 mg/g and 112.7 ± 13 mg/g. The data of this study have demonstrated that *Polygonum aviculare* L. herba extracts have high phenolics and flavonoid content, and produces valuable antioxidant activity (Hsu, 2006).

### Aqueous extracts:

The antioxidant activity of *Polygonum aviculare* L. herba was examined by spectrophotometric method using DPPH free radical (Gou *et al.*, 2011). The pressure-assisted water extraction (PAWE) technique was used to obtain higher extraction yields of plant and absorbance was measured using microplate reader. The efficient concentration (EC<sub>50</sub>) was expressed as the concentration (mg/mL) required for 50% reduction of DPPH free radical. The high antioxidant activity was observed at *Polygonum aviculare* L. herba extracted by the pressure-assisted water extraction (PAWE) technique, showing the lowest EC<sub>50</sub> value (0.09 mg/mL). For the standard curve gallic acid was used. The total phenolic amount was expressed as gallic acid equivalent of plant extract (mg GAE/g). The free radical scavenging activity correlated with the content of total phenols (71,72 mg GAE/g) of *Polygonum aviculare* L. herba (Gou *et al.*, 2011).

### Other extracts:

Dried *Polygonum aviculare* L. herba plant material extracted with 80% methanol was estimated among other 32 selected herbs for their antioxidant capacity by using the following methods: ABTS<sup>+</sup> (2,2-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid)), DPPH (1,1-diphenyl-2-picrylhydrazyl radical) and ferric reducing/antioxidant power (FRAP) expressed as TEAC (total equivalent antioxidant capacities). The data were expressed as  $\mu\text{M}$  trolox per 100 g dry weight (dw). The TEAC values were 19.2  $\mu\text{M}$  trolox/100 g dw for ABTS<sup>+</sup>, 141  $\mu\text{M}$  trolox/100 g dw for DPPH and 161  $\mu\text{M}$  trolox/100 g dw for FRAP. The total phenolic amount was expressed as gallic acid equivalent of plant extract (mg GAE/g). The total phenolics were 11.2 mg of GAE/100g of dry weight for the *Polygonum aviculare* L. herba measured by Folin–Ciocalteu colorimetric method. High levels of phenolics in *Polygonum aviculare* L. herba indicate remarkable antioxidant activity (Wojdyło *et al.*, 2007).

### Isolated constituents:

Granica *et al.* (2013a) investigated the antioxidant activity of 11 flavonol glucuronides (myricetin 3-O- $\beta$ -D-glucuronide, mearsetin 3-O- $\beta$ -D-glucuronide, quercetin 3-O- $\beta$ -D-glucuronide, isorhamnetin 3-O- $\beta$ -D-glucuronide, kaempferide 3-O- $\beta$ -D-glucuronide, kaempferol 3-O- $\beta$ -D-glucuronide, kaempferol 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide), isorhamnetin 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide), quercetin 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide), quercetin 3-O- $\beta$ -(3''-O-acetyl- $\beta$ -D-glucuronide), kaempferol 3-O- $\beta$ -(3''-O-acetyl- $\beta$ -D-glucuronide)) isolated from *Polygonum aviculare* L. herba. The *Polygonum aviculare* L. herba (1000 g) was powdered and extracted with solvents of rising polarity (petroleum ether, chloroform (CHCl<sub>3</sub>), ethyl acetate (AcOEt), acetone (Me<sub>2</sub>CO) and water (H<sub>2</sub>O)). 8 of flavonol glucuronides were reported for the first time from the *Polygonum* species (e.g. acetylated kaempferol, isorhamnetin glucuronides). All studied compounds at concentrations of 1 and 10  $\mu\text{M}$  significantly inhibited the production of reactive oxygen species (ROS). Quercetin 3-O- $\beta$ -D-glucuronide, quercetin 3-O- $\beta$ -(2''-O-acetyl- $\beta$ -D-glucuronide) and quercetin 3-O- $\beta$ -(3''-O-acetyl- $\beta$ -D-glucuronide) all at the concentration of 10  $\mu\text{M}$  strongly inhibited production of ROS with the effect comparable to quercetin that served as a control (Granica *et al.*, 2013a).

## **Vasorelaxant activity**

### *Ex vivo*

The vasorelaxant activity of hexane and *n*-butanol (*n*-BuOH) extracts of *Polygonum aviculare* herba was investigated on phenylephrine ( $3 \times 10^{-6}$  M) pre-contracted rat aortic tissues. The maximum relaxation obtained by hexane extract was 62.6 % and for *n*-BuOH extract was 89.7 %. The expressed vasorelaxant activity on endothelium –intact aortic tissues was in a dose-dependent manner. Removal of functional endothelium or pre-treatment of the inhibitor of nitric oxide synthase (aortic tissues with

NG-nitro-L-arginine methyl ester (L-NAME)) suppressed this effect indicating that relaxation of the vascular smooth muscle is realized via endothelium-dependent nitric oxide mechanism (Yin *et al.*, 2005).

### **Antifungal activity**

#### *In vitro*

The antifungal activity of *Polygonum aviculare* herba extracts (water, acetone, ethanol and chloroform) was tested on Fungal isolates (*Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger* and the yeast *C. albicans*) by the paper disc diffusion method using streptomycin as standard were used for comparison (Salama and Marraiki, 2010). Also a different concentrations of isolated panicudine dissolved in chloroform (400, 40, 4, 0.4 mg/g) were tested for antifungal activity by measurement of inhibition zone (Salama and Marraiki, 2010). The measurement of inhibition zone around each paper disc demonstrated that chloroform extract show a good antimicrobial activity against all tested fungi (diameter of inhibition zone - 17 mm against *Aspergillus flavus*, 18 mm against *Aspergillus fumigatus*, 14 mm against *Aspergillus niger*) except *C. albicans* (diameter of inhibition zone 0 mm). The next potent antimicrobial activity was expressed by the water extracts (diameter of inhibition zone - 14 mm against *Aspergillus flavus*, 15 mm against *Aspergillus fumigatus*, 13 mm against *Aspergillus niger*, 0 mm against *Candida albicans*), then followed by the ethanol extracts and, finally by the acetone extracts (Salama and Marraiki, 2010).

### **Anti-obesity activity**

#### *In vitro*

Ethanol extract of *Polygonum aviculare* herba was tested *in vitro* for enzymatic lipase activity in pancreatic lipase inhibition assay. The results showed that inhibition of the lipid accumulation in 3T3-L1 adipocytes *in vitro* was 21.2 %, indicating anti-obesity activity for *Polygonum aviculare* herba (Roh and Jung, 2012).

#### *In vivo*

The antiobesity effects of ethanol extract of *Polygonum aviculare* herba was explored in high-fat diet (HFD-) induced obese mice. The results indicated that administration of *Polygonum aviculare* herba extract to HFD-induced obese mice significantly decreased adipose tissue weight, body weight gain, adipocyte size, and decreased lipogenic gene expression. The levels of serum triglyceride, leptin, and MDA were lowered as well as 3T3-L1 adipocyte differentiation was inhibited. The data obtained suggests that exerted antiobesity effects in HFD-induced obese mice is via the suppression of lipogenesis in adipose tissue and increased antioxidant activity (Sung *et al.*, 2013)

### **Anti-atherosclerotic effects**

#### *In vitro and in vivo*

The ethanol extract of *Polygonum aviculare* L. herba was studied in atherosclerotic (ApoE KO) mice that were fed with a Western diet (WD) alone or with *Polygonum aviculare* L. ethanol extract (50 and 100 mg/kg) or a statin (10 mg/kg) for 12 weeks. Results show that *Polygonum aviculare* L. ethanol extract and statin intake induced less body weight, lowered serum lipid levels and blood pressures and had less adipose tissue than the WD group mice. Examination of a staining of the aorta and adipose tissue, expression levels of adhesion molecules, and the effect of the NF- $\kappa$ B activity demonstrated that aorta ICAM-1, VCAM-1 and NF- $\kappa$ B levels were decreased by *Polygonum aviculare* L. ethanol extract in a dose-dependent manner. Also *Polygonum aviculare* L. ethanol extract and statin reduced atherosclerotic plaque and adipocyte size compared to the Western diet group and decreased

phosphorylation of MAPK pathway components in the aorta of *Polygonum aviculare* L.-treated mice, suggesting that anti-atherosclerotic effects of the ethanol extract of *Polygonum aviculare* L. herba are mediated via a MAPK pathway- dependent mechanism (Park *et al.*, 2014).

### **Anticancer effects**

#### *In vitro*

Anticancer effects of *Polygonum avicular* herbal methanol extracts using different concentrations (50, 100, 150, 200, 250, 300,350 400 ng/μl) was investigated in MCF-7 cell line (human breast cancer cell line). Cell proliferation and apoptosis were evaluate by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazoliumbromide) assay and Flow Cytometry, respectively. It was found that *Polygonum avicular* herbal methanol extract induced cytotoxicity in MCF-7 cell line at concentrations higher than 300 ng/μl and it was corresponding to the highest rate of cell death measured by Trypan Blue and MTT assays (Roudkenar *et al.*, 2011).

Methanol extracts of *Polygonum aviculare* herba of various concentration (50, 100, 250, 500, 1000 mg/ml) was tested on Cell lines nalm-6 (pre B-cell leukaemia). Trypan blue method for assessing the viability of the cells and to evaluate the cytotoxic effect of the MTT assay (3 -(4, 5 Dimethylthiazol -2-yl) was used. The results of the MTT assay demonstrated that with increasing concentrations cells increased death rate indicating that methanolic extract of *Polygonum aviculare* herba has cytotoxic effect on nalm-6 cell line (Kazemivash and Jamali 2013).

MCF-7 (human breast cancer cell line) cells were treated with Different concentrations (50, 100, 150, 200, 250, 300,350 400 ng/μl) of *Polygonum aviculare* methanol extract. Then RT-PCR (real-time polymerase chain reaction test) was also carried out to evaluate the expression of apoptotic genes.

RT-PCR results showed up-regulation of P53 and down-regulation of Bcl-2 proteins which indicated the ability of *Polygonum aviculare* to induce apoptosis in MCF-7 cells and confirmed its anticancer property (Roudkenar *et al.*, 2011).

### **3.1.3. Safety pharmacology**

No data available.

### **3.1.4. Pharmacodynamic interactions**

No data available.

### **3.1.5. Conclusions**

Significant anti-inflammatory, antioxidative and antibacterial effects of *Polygonum aviculare* L. herba extracts (water, acetone, ethanol and chloroform) and isolated constituents (panicudine, flavonol glucuronides, avicularin) have been demonstrated in the experimental models *in vitro*, *ex vivo* and *in vivo*.

The aqueous extracts of *Polygonum aviculare* L. herba as well as fractions and isolated individual substances in some studies shown less potent activity than chloroform extracts but higher activity than ethanol and acetone extracts (Salama and Marraiki, 2010). It has been pointed out in the several studies that the high phenolics and flavonoid content present in the leaves and stem of the *Polygonum aviculare* L. is responsible for the most of important pharmacological effects of *Polygonum aviculare* L. herba.



The historical medicinal use of *Polygonum aviculare* L. herba described in several monographs and well-known handbooks as well as indications used for the products available on the EU market for the traditional herbal medicine use correspond with the effects obtained in the non-clinical studies and are plausible supporting the traditional use of the herbal substance and preparation in the following indications:

- for symptomatic treatment of minor inflammations in the mouth or the throat;
- for the symptomatic treatment of common cold;
- to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

Other effects not related to the indications proposed for the *Polygonum aviculare* L. herba in the monograph but demonstrated in the non-clinical studies are anti-obesity activity, antifungal, vasorelaxant, anti-atherosclerotic and anticancer effects.

None of the reported non-clinical pharmacological studies described any cause for safety concern.

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

Tissue (heart, liver, spleen, lung, kidney and bladder) distribution of avicularin isolated from *Polygoni avicularis* herba after a single iv administration in rat was measured by HPLC method. The concentration of avicularin in above mentioned tissues showed significant diversity within 60 min. Determination of avicularin indicated that kidney and bladder showed the highest concentrations of this compound (Xu et al., 2012).

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

#### **3.3.1. Single dose toxicity**

No data available.

#### **3.3.2. Repeat dose toxicity**

Female Wistar rats were gavaged with *Polygonum aviculare* herba extract (1 ml) for 10 days. After 10 days rats were sacrificed and samples of brain - hypothalamus, adrenal glands, liver, kidney and small intestine (duodenum) were collected for further histological analysis using hematoxylin – eosine staining emphasizing the neuro – endocrine – pituitary – adrenal axis reaction as well as activity of enzymes (lactate dehydrogenase, succinate-dehydrogenase, Mg-dependent adenosine triphosphatase, cytochromoxidase) were investigated. The obtained results indicated that *Polygonum aviculare* herba extract did not produces any pathological effects at the neuro-endocrine axis level and in the metabolic studied organs (Roman *et al.*, 2008).

#### **3.3.3. Genotoxicity**

No data available.

### 3.3.4. Carcinogenicity

No data available.

### 3.3.5. Reproductive and developmental toxicity

No data available.

### 3.3.6. Local tolerance

No data available.

### 3.3.7. Other special studies

#### Cytotoxicity studies

Dose-dependent protective effect of *Polygonum aviculare* L. herba aqueous extracts was quantitatively evaluated on acetaminophen-induced cytotoxicity in human embryonic kidney HEK293 cells using an MTS (cell viability) assay. *Polygonum aviculare* herba extracts had significant recovery effect on acetaminophen-induced damage in HEK 293 cells. Dose response non-linear regression analysis demonstrated that *Polygonum aviculare* herba extracts had a strong recovery effect rate (98%) on acetaminophen-induced damage in HEK 293 cells. The EC<sub>50</sub> value was 0.1 ng/mL (Sohn *et al.*, 2009).

The cytotoxic effect of 11 flavonol glucuronides (myricetin 3-O-β-D-glucuronide, mearsetin 3-O-β-D-glucuronide, quercetin 3-O-β-D-glucuronide, isorhamnetin 3-O-β-D-glucuronide, kaempferide 3-O-β-D-glucuronide, kaempferol 3-O-β-D-glucuronide, kaempferol 3-O-β-(2"-O-acetyl-β-D-glucuronide), isorhamnetin 3-O-β-(2"-O-acetyl-β-D-glucuronide), quercetin 3-O-β-(2"-O-acetyl-β-D-glucuronide), quercetin 3-O-β-(3"-O-acetyl-β-D-glucuronide), kaempferol 3-O-β-(3"-O-acetyl-β-D-glucuronide)) isolated from *Polygonum aviculare* L. herba was investigated on human neutrophils by flow cytometry with propidium iodide assay.

The data show that these compounds did not influence the viability of neutrophils at concentrations up to 30 μM. The camptothecin at the concentration of 10 μM was used as a positive control (Granica *et al.* 2013a).

### 3.3.8. Conclusions

The data on toxicology of *Polygonum aviculare* herba and relevant preparations are limited. The repeated dose study *in vivo* consuming *Polygonum aviculare* herba extract for 10 days did not produce any pathological effects in brain - hypothalamus, adrenal glands, liver, kidney and small intestine (duodenum).

Oral administration of *Polygonum aviculare* herba can be regarded as safe at traditionally used doses. Due to the lack of data on genotoxicity a list entry cannot be proposed.

## 3.4. Overall conclusions on non-clinical data

Non-clinical data on *Polygonum aviculare* herba support the traditional use of the herbal substance and preparation the proposed indication.



Pharmacokinetics and interactions has not been fully evaluated. Limited data available indicated that the highest concentrations of isolated compound of *Polygoni avicularis* herba avicularin were in kidney and bladder after 24 hr of administration are kidney and bladder (Xu et al., 2012).

**There are no data available regarding single dose toxicity and non-clinical information on the safety of *Polygoni avicularis* herba.**

Other specific studies demonstrated protective effect on acetaminophen-induced cytotoxicity in human embryonic kidney cells (Sohn *et al.*, 2009) and no cytotoxic effect on human neutrophils (Granica *et al.* 2013a).

**Tests on genotoxicity and carcinogenicity have not been performed.**

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

The long-term widespread use in the European Union and available data indicate no toxicological concern and potential risk associated with *Polygonum aviculare* herba use.

Oral and oromucosal administration of *Polygonum aviculare* herba can be regarded as safe at traditionally used doses.

## **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**

No data available.

#### **4.2.1. Dose response studies**

No data available.

#### **4.2.2. Clinical studies (case studies and clinical trials)**

The effectiveness of *Polygonum aviculare* L. extract (a natural Mexican *Sanguinaria* extract, extraction solvent ethanol) against gingivitis has been studied in 60 male volunteers with gingivitis aged 18 to 25 years. However, the methodology of the study is weak; for instance, parts of the *Polygonum aviculare* L. used in this study are not clearly specified. The following inclusion criteria were used: at least 24 natural teeth and gingivitis. The following exclusion criteria were introduced: current illness, a history of oral mucosal tissue reaction or known sensitivity to oral rinses, orthodontic appliances, periodontitis, continuous antibiotic usage and unwillingness to use the oral rinse and to adhere strictly to the

examination procedures. Over a period of 2 weeks no tooth-brushing was allowed instead volunteers of this study use *Polygonum aviculare* L. extract (1 mg/lm) as oral rinse twice daily. The Löe and Silness Gingival Index was recorded at day 0, the study population had a gingival index mean of 1.056 (S.D.  $\pm$  0.074) with a maximum value of  $\bar{x}$  = 1.290 and a minimum value of  $\bar{x}$  = 0.920. The O'Leary Plaque Index had an arithmetic mean of  $\bar{x}$  = 91.389 (S.D.  $\pm$  9.168) with a maximum value of  $\bar{x}$  = 100 and a minimum value of  $\bar{x}$  = 62.50. During the treatment the prevalence of gingivitis decreased, demonstrating  $\bar{x}$  = 1.017 (S.D.  $\pm$  0.032) on day 7, an  $\bar{x}$  = 1.012 (S.D.  $\pm$  0.32) on day 11, and an  $\bar{x}$  = 1.011 (S.D.  $\pm$  0.32) on day 14 ( $P \leq 0.05$ ). The obtained results indicated the usefulness of the *Polygonum aviculare* L. as a supportively in the therapy of gingivitis In contrast, the results of the plaque index shown the significant increase from day 0 ( $\bar{x}$  = 91.38) to day 14 ( $\bar{x}$  = 98.69) ( $P \leq 0.05$ ), however, the consistency of this plaque permitted its mechanical flushing easily (Begné et al. 2001).

Table 5: Clinical studies on humans, in gingivitis

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Outcomes	Statistical analysis e.g. Jadad score	Clinical relevance
<p>Treatment of gingivitis using <i>Polygonum aviculare</i> L.</p> <p>Efficacy study</p> <p>Begn� et al. 2001</p>	<p>open study</p> <p>O'Leary Plaque Index and the L�e and Silness Gingival Index were recorded at day 0</p> <p>duration: 2 weeks</p> <p>evaluation performed on days 7, 11 and 14</p> <p>no tooth-brushing was allowed</p>	<p>Treatment: extract of <i>Polygonum aviculare</i> L. (1 mg/lm) as oral rinse twice daily for 2 weeks</p>	<p>60 patients with gingivitis</p> <p>the L�e and Silness Gingival Index had a mean of 1.056 (S.D.±0.074), a maximum value was <math>\bar{x} = 1.290</math>, a minimum value was <math>\bar{x} = 0.920</math></p> <p>the O'Leary Plaque Index had an arithmetic mean of <math>\bar{x} = 91.389</math> (S.D. ± 9.168) with a maximum value of <math>\bar{x} = 100</math> and a minimum value of <math>\bar{x} = 62.50</math>.</p> <p>age: 18 to 25 sex: male</p> <p>9 drop-out (15%) reason: unknown</p>	<p>Patients with gingivitis</p> <p>inclusion criteria: at least 24 natural teeth and gingivitis</p> <p>exclusion criteria: current illness, a history of oral mucosal tissue reaction or known sensitivity to oral rinses, orthodontic appliances, periodontitis, continuous antibiotic usage and unwillingness to use the oral rinse and to adhere strictly to the examination procedures required for the study</p>	<p>Improvement: the prevalence of gingivitis decreased, demonstrating <math>\bar{x} = 1.017</math> (S.D. ± 0.032) on day 7, an <math>\bar{x} = 1.012</math> (S.D. ± 0.32) on day 11, and an <math>\bar{x} = 1.011</math> (S.D. ± 0.32) on day 14.</p> <p>whereas the plaque index increased significantly from day 0 (<math>\bar{x} = 91.38</math>) to day 14 (<math>\bar{x} = 98.69</math>) (<math>P \leq 0.05</math>)</p> <p>Good tolerability,  no adverse effects</p>	<p>Wilcoxon Matched-Pairs at day Wilcoxon Matched-Pairs Signed-Ranks test (<math>P \leq 0.05</math>) (SPSS:PC package)</p>	<p>Methodology of the study is weak, part of the plant studied is not clear</p>

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

No data available.

### **4.4. Overall conclusions on clinical pharmacology and efficacy**

One clinical study has been reported to investigate the efficacy of *Polygonum aviculare* L. in gingivitis. The obtained results have demonstrated the significant decreased in prevalence of gingivitis during the two weeks twice daily usage of *Polygonum aviculare* L. extract. However, the methodology of the study is weak, not clearly indicating the parts of the plant used in the study as well as there are not currently preparations for the treatment in gingivitis available in ES market neither there are strong literature data supporting it. Therefore the indication of *Polygonum aviculare* L. in gingivitis is not currently supported in the monograph.

For the indications proposed in the monograph no data from clinical studies are available on pharmacodynamics, pharmacokinetic, dose-response relationship and on clinical studies in special populations, such as elderly and children related to the indications of traditional use; therefore in accordance with Directive 2001/83/EC the well-established use cannot be supported.

Whereas the plausibility of efficacy for the traditional use of *Polygonum aviculare* L. herba for the symptomatic treatment of minor inflammations of the mouth or the throat, the relief of symptoms in coughs and colds and to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints is based on long-standing use and availability in EU as well as sufficiently support and well documented by a number of well-known handbooks and monographs (Hoppe 1942; Haverland, 1962; Pētersone, 1961; Rubine et al. 1977; Blumenthal et al., 1998; Weiss and Fintelmann, 2000; Wichtl, 2004; Gehrman et al., 2005; Wyk and Wink, 2005; WHO monographs NIS 2010 etc). The traditional use is also supported by pharmacological data, see section 3.

Overall, the medicinal use of *Polygonum aviculare* L. herba has to be regarded as traditional and allows the development of a European Union herbal monograph on the traditional use.

## **5. Clinical Safety/Pharmacovigilance**

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

There is only one clinical study on *Polygonum aviculare* L. use in gingivitis for two weeks available (Begné *et al.* 2001). Besides the efficacy data, a good tolerability and no adverse effects were mentioned in the publication. However, in general the methodology of this study is weak, not clearly indicating the parts of the plant used in the study. Gingivitis is not the indication proposed in the monograph.

Table 6: Clinical safety data from clinical trials

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
<p>Treatment of gingivitis using <i>Polygonum aviculare</i> L.</p> <p>Efficacy study</p> <p>Begné <i>et al.</i> 2001</p>	<p>open study</p> <p>O'Leary Plaque Index and the Löe and Silness Gingival Index were recorded at day 0</p> <p>duration: 2 weeks</p> <p>evaluation performed on days 7, 11 and 14</p> <p>no tooth-brushing was allowed</p>	<p>Treatment: extract of <i>Polygonum aviculare</i> L. (1 mg/lm) as oral rinse twice daily for 2 weeks</p>	<p>60 patients with gingivitis</p> <p>the Löe and Silness Gingival Index had a mean of 1.056 (S.D.±0.074), a maximum value was <math>\bar{x}=1.290</math>, a minimum value was <math>\bar{x}=0.920</math></p> <p>the O'Leary Plaque Index had an arithmetic mean of <math>\bar{x}=91.389</math> (S.D. ± 9.168) with a maximum value of <math>\bar{x}=100</math> and a minimum value of <math>\bar{x}=62.50</math>.</p> <p>age: 18 to 25 sex: male</p> <p>9 drop-out (15%) reason: unknown</p>	<p>Patients with gingivitis</p> <p>inclusion criteria: at least 24 natural teeth and gingivitis</p> <p>exclusion criteria: current illness, a history of oral mucosal tissue reaction or known sensitivity to oral rinses, orthodontic appliances, periodontitis, continuous antibiotic usage and unwillingness to use the oral rinse and to adhere strictly to the examination procedures required for the study</p>	<p>No adverse effects</p> <p>Good tolerability</p>	<p>Methodology of the study is weak, part of the plant studied is not clear</p>

## **5.2. Patient exposure**

No exact data on patient exposure are available. On the basis of the use in some Member States over a period of more than 30 years a significant exposure can be assumed.

## **5.3. Adverse events, serious adverse events and deaths**

Any kinds of adverse events or deaths have not been reported so far.

## **5.4. Laboratory findings**

No data available.

## **5.5. Safety in special populations and situations**

No data available.

### **5.5.1. Use in children and adolescents**

The use in children has not been investigated therefore the use in children under 12 years of age is not recommended. For the adolescents the use is supported through the traditional use.

### **5.5.2. Contraindications**

Hypersensitivity to the active substance.

### **5.5.3. Special Warnings and precautions for use**

The use in children under 12 years of age has not been established due to lack of adequate data.

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

### **5.5.4. Drug interactions and other forms of interaction**

No data available.

### **5.5.5. Fertility, pregnancy and lactation**

No data on fertility is available. As well as no data are supporting the safety use of *Polygonum aviculare* L. herba during pregnancy and lactation. Therefore it should not be recommended during pregnancy and lactation.

### **5.5.6. Overdose**

No data available.

### **5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability**

No data available.

### 5.5.8. Safety in other special situations

No data available.

## 5.6. Overall conclusions on clinical safety

Any kinds of adverse events or deaths have not been reported so far. Conventional clinical safety data are absent. There is only one clinical study on the efficacy of *Polygonum aviculare* L. on gingivitis demonstrating good safety profile. However, the methodology of the study is weak, not clearly indicating the parts of the plant used in the study.

For the indications proposed in the monograph there are no clinical safety data for *Polygonum aviculare* L. herba available. Even clinical data on use in children or adolescents are not available, there are products used in EU market with indications: a) traditional herbal medicinal product used for the relief of symptoms of common cold and b) traditional herbal medicinal product used in mild urinary tract inflammation cases. In both indications mentioned above, the use is intended also for adolescents.

There are no data on reproductive and developmental toxicity therefore the use during pregnancy cannot be recommended.

The duration of use is limited:

- to one week for the symptomatic treatment of minor inflammations in the mouth or the throat and used the relief of symptoms of common cold;
- two weeks in order to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

A long-standing medicinal use and experience of *Polygonum aviculare* L. herba is documented within the EU in accordance with Directive 2004/24/EC. The available information on present use and historical data indicate that there are no safety concerns of usage of *Polygonum aviculare* L. herba in humans if used in accordance with the specified indications and doses, and the oral administration of *Polygonum aviculare* L. herba can be regarded as safe.

## 6. Overall conclusions (benefit-risk assessment)

Well-established use as defined in Directive 2001/83/EC cannot be accepted for *Polygonum avicularis* L., herba due to the lack of data from clinical studies with recognised clinical efficacy and acceptable safety profile.

Based on the references available and the information provided by the National Competent Authorities the presence of medicinal products on the European market throughout a period more than 30 years, including at least 15 years within the EU is substantiated. The traditional medicinal use of *Polygonum avicularis* L., herba according to Directive 2004/24/EC is fulfilled.

The efficacy of *Polygonum aviculare* L., herba for the traditional medicinal use in the European Union monograph is plausible on the basis of long-standing use and experience for the following indications:

*For oromucosal use:*

'Traditional herbal medicinal product for symptomatic treatment of minor inflammations in the mouth or the throat'.

*In adolescents, adults and elderly:*

Single dose: 1.5 g in glass of water (200-250ml) as freshly prepared decoction for rinsing or gargling between meals;

4 - 5 times daily;

Daily dosage: 6 – 7.5 g;

Duration of use: 1 week

*For oral use:*

'Traditional herbal medicinal product used for the relief of symptoms of common cold'.

*In adolescents, adults and elderly:*

Single dose: 1.5 - 2 g of the comminuted herbal substance in 150 ml of boiling water as a herbal tea for oral use;

3 - 4 times daily;

Daily dosage: 4.5 - 8 g;

Duration of use: 1 week.

*For oral use:*

'Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints'.

*In adolescents, adults and elderly:*

Single dose

Herbal tea: 3 g of the comminuted herbal substance in 200 ml of water as a decoction for oral use;

2 times daily;

Daily dosage: 6 g

Duration of use: 2 weeks

The indications fulfil the requirements for traditional use in that they are suitable for self-medication.

Due to lack of adequate data, *Polygonum aviculare* L., herba cannot be recommended for oral use in children under 12 years of age.

Studies on genotoxicity, carcinogenicity, reproductive and developmental toxicology of *Polygonum aviculare* L., herba have not been conducted. A European Union list entry is not supported due to lack of data on genotoxicity for *Polygonum aviculare* L., herba.



There is no information on reproductive and developmental toxicity of *Polygonum aviculare* L., herba available, therefore the use during pregnancy and lactation due to insufficient data are not recommended. No data on fertility are available.

No adverse effects have been reported in the documentation of medicinal use. The history of long-term and present use in humans in the European Union and the currently available information indicate no safety concerns associated with the oral or oromucosal use of *Polygonum aviculare* L., herba in recommended dosages under the conditions specified in the monograph.

The therapeutic areas for browse search on the EMA website are 'Mouth and throat disorders', 'Cough and cold' and 'Urinary tract and gynaecology disorders'.

No constituents with known therapeutic activity are considered by the HMPC.

## **Annex**

### ***List of references***