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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., herba

Final

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

Herbal substances (binomial scientific name of the plant, including plant part)	<i>Sideritis scardica</i> Griseb.; <i>Sideritis clandestina</i> (Bory & Chaub.) Hayek; <i>Sideritis raeseri</i> Boiss. & Heldr.; <i>Sideritis syriaca</i> L., herba
Herbal preparation	Comminuted herbal substance
Pharmaceutical form	Comminuted herbal substance as herbal tea for oral use
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# 1. Introduction

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

- Herbal substance(s)

There is not any existing monograph in National Pharmacopoeias or National Codexes currently used in the Member States or any other monograph, on *Sideritis herba*.

***Sideritis*** (also known as ironwort, mountain tea and shepherd's tea) is a genus of flowering plants known for their traditional use as aromatic herbal tea. *Sideritis* plants are abundant in Mediterranean regions, the Balkans and the Iberian Peninsula but can also be found in Central Europe and West Asia (Bojovic *et al.*, 2011; Petreska *et al.* 2015).

***Sideritis*** plants are found on rocky slopes at elevations over 1000 m; they are hardy flowering perennials. Only some of the species are cultivated, among which *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., in Greece and Bulgaria. The other species are mainly harvested from the wild (Bojovic *et al.*, 2011).

*Sideritis* (Labiatae - Lamiaceae) has been characterised as a genus with more than 150 perennial and annual vegetal species widely distributed in the Mediterranean area, together with the Canary and Madeira islands (Bojovic *et al.*, 2011).

The plants are growing wild in the Balkan peninsula while in Greece alone, 17 different species are indigenous, fragrant and very productive such as: *Sideritis athoa* (growing on Mount Athos), *Sideritis clandestina* (growing on the especially rough Mount Helmos and Taygetos in the Peloponnese), *Sideritis scardica* (on Mount Olympus), *Sideritis raeseri* (on Mount Parnassus), *Sideritis syriaca* (on the mountains of Crete, known as malotira) and *Siderities euboea* (on the mountains of the Euboea island). Among these *Sideritis raeseri*, *Sideritis scardica*, *Sideritis syriaca* and *Sideritis clandestina* can be found in wild as well as cultivated (Heywood, 1972).

According to Flora Europaea, all the following species of *Sideritis* species belong to section Empedoclia (Rafin.) Benth. Perennial herbs with a woody base. Bracts entire, usually not leaf-like (Heywood, 1972): *Sideritis syriaca* L.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis scardica* Griseb.; *Sideritis perfoliata* L.; *Sideritis montana* L. (*subsp. montana*; *subsp. remota*); *Sideritis lanata* L.; *Sideritis romana* L. (*subsp. romana*; *subsp. purpurea*) and *Sideritis curvidens* (Heywood, 1972).

Geographically spread as following

- ***Sideritis scardica*** Griseb.: on rocky areas and alpine regions North Greece up to Olympos mountain and Pelion mount, known also as tea of Olympos. The plant grows in mountain rocks (central part of Balkan Peninsula, Greece, Albania, FYROM (Former Yugoslavian Republic of Macedonia), Bulgaria, Serbia and Turkey) (Heywood, 1972; Petreska *et al.*, 2015)
- ***Sideritis raeseri*** Boiss. & Heldr.: on rocky and areas of North Greece, known as tea of Velouchi and Parnassos mount (Heywood, 1972).
- ***Sideritis syriaca*** L., growing wild and also cultivated in the island of Crete, known as malotira male (illness) and tirare (pull). Widespread in mountain rocks South Europe from Sicilia to Krym (Heywood, 1972).

- ***Sideritis clandestina*** (Bory & Chaub.) Hayek endemic to the South Peloponnesus, in Greece (Heywood, 1972).

***Sideritis syriaca*** L. (Cretan mountain tea); (incl. *Sideritis cretica* Boiss., non L., *Sideritis raeseri* Boiss. & Heldr., *Sideritis sicula* Ucria, *Sideritis taurica* Stephan ex Willd.). Grey or white lanate perennial 10-50 cm. Lower leaves 10-60 x (5-)6-20 mm, oblong to narrowly obovate, entire, crenulated or denticulate; middle and upper leaves up to 80 x 18mm, linear-lanceolate or oblong entire. Verticillasters 5-20, 6 - to 10 flowered, mostly distant, rarely all crowded. Middle bracts 6-12 mm (including acumen), usually shorter than or equalling flowers, suborbicular; acumen 2-3 mm. Calyx 7-12 mm; teeth 2.5-5 mm, half as long to almost as long as tube. Corolla 9-15 mm yellow.  $2n=24$ . *S. syriaca* had been noted as a synonym of *S. raeseri* but since *S. raeseri* have been accepted as separate species for the Balkan Peninsula. (Petreska *et al.*, 2015) (Heywood, 1972).

A variable species, usually divided into several species and subordinate taxa. Within restricted part of its range it is often possible to distinguish many of the local populations from each other, but when the whole range of variation is taken into consideration no satisfactory subdivision seems possible.

***Sideritis clandestina*** (Bory & Chaub.) Hayek. Yellowish or grey-lanate perennial 15-40 cm. Lower leaves 25-50 x 8-20 mm, oblong-spathulate to obovate, entire or crenulated; middle and upper leaves 30-70 x 6-12 mm, linear to oblong-elliptical, entire. Verticillasters 4-20, many-flowered, crowded or to lower 1-3 distant. Middle bracts 15-25 mm (including acumen), exceeding the flowers, broadly ovate to suborbicular; acumen 4-10 mm, sparsely or densely lanate. Calyx 9-11 mm; teeth 3.5-4.5 mm, slightly shorter than tube. Corolla 10-15 mm, yellow (Heywood, 1972). Plants from Taygetos (var. *clandestina*) have a grey indumentum, linear to linear - oblong middle and upper leaves 10-20 verticillasters with the uppermost crowded and densely lanate bracts with acumens 6-10 mm. Those from Killini (var. *cyllenea* (Heldr. ex Boiss.) Hayek) have a yellowish indumentum, oblong-elliptical middle and upper leaves, 4-10 distant verticillasters and sparsely lanate bracts with acumen 4-6 mm.

***Sideritis scardica*** Griseb. It is like *Sideritis clandestina* but usually densely white-lanate; lower leaves 40-80 x 6-20 mm oblong-lanceolate; verticillasters crowded into a dense spike; middle bracts 12-20 mm, suborbicular-cordate, sparsely lanate, abruptly acuminate with acumen 2-4 mm; calyx 9-12 mm; calyx-teeth 3-4 (-6) mm, usually about half as long as tube.  $2n=32$  (Heywood, 1972). *Sideritis scardica* Griseb. was described for the first time in mountains of geographic area of Macedonia (Greece, FYROM (Former Yugoslavian Republic of Macedonia), Bulgaria) in the mid - 19<sup>th</sup> century by the botanist A. Grisebach, who gave the name of the mountain, where the plant was found (Grisebach, 1844 cited in Yaneva & Balabanski, 2013; Heywood 1972). Several authors have been described the species. Hardy perennial with creeping roots.

Stems - in the bottom are woody, 15-50 cm tall, flower bearing stems (sprigs)-erect or prostrate, 4-angle; simple or branched (usually unbranched). Leaves - opposite, entire (smoothed) or serrated leaf blade, leaves vary by their shape: from oblanceolate (long lanceolate), to obtuse - in the lowest veins; to longer in the middle veins; to lanceolate (linear lanceolate) - acute in the highest veins. Lower leaves have short stalk, 40-80 mm long, 6-20 mm wide. Upper leaves from the 4<sup>th</sup> vein upward are prostrate as the stalk is shortened gradually from lower to upper leaves. Bracts have almost elliptical shape (wide heart shape at the base, acute pointed to the apex), with gentle skin consistency. When ripening they get lemon - yellow colour. In the first vein they are 38 mm long and 50-80 mm wide as to the apex of the inflorescence their dimensions decrease. Flowers are gathered in dense spike-like inflorescences, 50-80 mm long, about 30 mm wide, receptacle is tube cup-shaped, with 10 veins and 5 equal teeth, pubescent and coated by fine intertwined hairs. The whorl is yellow. With a tube hidden in the receptacle, two lipped with three-lobe lower lip. Four stems are hidden in the tubes of the whorl. The fruit is dry, decomposed in 4 nuts. Leaves and stem are white, woolly - villous. Depending on the

sea level and climate properties the plant comes out in blossom from the end of June to the beginning of September. Its smell is pleasant, and the taste is slightly bitter (Heywood, 1972).

### Chemical constituents

Terpenes, flavonoids, essential oils, iridoids, coumarins, lignans and sterols have been reported from the genus *Sideritis*. Differences in chemical composition are observed between the *Sideritis* spp. and the regions where they grow (Bojovic *et al.*, 2011). According to existing references, the following secondary metabolites have been isolated from Mediterranean *Sideritis* species (Petreska *et al.*, 2011b; Todorova & Trendafilova, 2014; Papaefstathiou *et al.*, 2014; Vassilopoulou *et al.*, 2013):

- **Monoterpenes**
- **Diterpenes**

Many diterpenes (*ent*-kaurene derivatives) have been described for *Sideritis scardica* as isolinearol, leucanthol 18-monoacetate, siderol, sideroxol, epoxysiderol and eubol (Venturella & Bellino, 1979 cited in Fraga, 2012).

- **Sesquiterpenes**
- **Flavonoids**

Flavonoid 7-*O*-diglycosides, two types of flavones, 8-OH (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-OH (apigenin and luteolin), 8-OH (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-OH (apigenin and chryseriol); flavonoid 7-*O*-diglycoside; six acetylated flavonoid 7-*O*-diglycosides of apigenin and isoscutellarein and four isomers of apigenin 7-*O*-(coumaroyl) glucopyranoside together with apigenin 7-*O*-acetylcoumaroyl – allosyl (1 ? 2) glucoside (Petreska *et al.*, 2011b; Bojovic *et al.*, 2011; Yaneva & Balabanski, 2013; Fraga, 2012; Vassilopoulou *et al.*, 2013; Papaefstathiou *et al.*, 2014).

- **Triterpenes, Coumarins**
- **Sterols**

Campesterol (7.6%), stigmasterol (28.4%) and  $\beta$ -sitosterol

- **Phenylpropanoids**

Hydroxycinnamic acids, phenylethanoid glycosides

- **Minerals**

Twenty minerals in dried over-ground parts of the plants and in water tea-infusions were determined. As most abundant the following minerals were K > Ca > Mg > P > Fe > Al > Na and microelements as well as designated toxic elements were given in the following order: Zn > Mn > B > Ba > Cu > Sr > Li > Ni > Cr > Co, and Cd > Pb > As, respectively. In case of water tea-infusions a large portion of K, P, Na, Cu and Pb, but smaller amounts of the other elements have been found (Bojovic *et al.*, 2011; Yaneva & Balabanski, 2013).

Especially, the investigation of *Sideritis scardica*, and *Sideritis raeseri* revealed the presence of a complex profile of hydroxycinnamic acids, phenylethanoid glycosides and both acetylated and non-acetylated flavonoid 7-*O*-glycosides. Two types of flavones, 8-OH (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-OH (apigenin and luteolin), have been confirmed. All the flavonoid glycosides detected were 7-*O*-allosyl-(1,2)-glucoside derivatives, 5,8 - dihydroxyflavones with a different substitution in the B-ring. Differences in the phenolic profile of hydroxycinnamic acid and flavonoid 7-*O*-glycosides were found between *Sideritis scardica* and *Sideritis raeseri*. Flavonoid 7-*O*-

diglycosides were not detected in the methanol extract of *Sideritis scardica* (Bojovic *et al.*, 2011). The identification of the flavonoids in populations of *Sideritis scardica* and *Sideritis raeseri* in central Balkan region (Former Yugoslavian Republic Of Macedonia) and the presence of two types of flavones, 8-OH (hypolaetin and isoscutellarein and their methoxy derivatives) and 5,7-OH (apigenin and chryseriol), have been confirmed, and the possibility of distinguishing between the two studied species (*Sideritis scardica* and *Sideritis raeseri*) has been suggested (Janeska *et al.*, 2007 in Bojovic *et al.*, 2011). Verbascoside, leucoscweptoside, martynoside and lavandulifolioside were determined to be the most important compounds with respect to their pharmacological properties (Ertan *et al.*, 2001; Ezer *et al.*, 1992; Pinar *et al.*, 2004; Rodriguez *et al.*, 2000, all cited in Bojovic *et al.*, 2011).

Coumarins and other aromatic derivatives such as the verbascoside, leucoseptoside A, and tentatively, forsythoside A, alyssonoside and echinacoside, have been identified as components of *Sideritis raeseri* Boiss. *et* Heldr. and *Sideritis scardica* L. from FYROM (Petreska *et al.*, 2011b; Koleva *et al.*, 2003; Fraga, 2012).

An evaluation with detailed information on the content of phenolic compounds, terpenoids, hydrocarbons and related compounds, as well as essential oil composition, of *Sideritis scardica* and *Sideritis raeseri* Boiss. & Heldr., from Greece, Bulgaria and FYROM), was published by Todorova and Trendafilova in 2014 (Todorova & Trendafilova, 2014; Petreska *et al.*, 2011b; Kostadinova *et al.*, 2007; Yaneva & Balabanski, 2013). For *Sideritis scardica* the first phytochemical analysis was performed by Bojchinov in 1943 (Bojchinov, 1943 cited in Yaneva & Balabanski, 2013).

In a recent study (Vassilopoulou *et al.*, 2013) the phytochemical composition of herbal tea from *Sideritis clandestina* (Bory & Chaub.) Hayek was studied. The phytochemical profile of the *Sideritis clandestina* tea was determined by liquid chromatography-UV diode array coupled to ion-trap mass spectrometry with electrospray ionisation interface (LC/DAD/ESI-MS). The identified compounds were classified into several natural product classes: quinic acid derivatives, iridoids, phenylethanol glycosides and flavonoids. The LC/DAD/ESI-MS analysis of the aqueous extract led to the separation and identification of the majority of the extract components, seventeen in total, which belonged to several classes of secondary metabolites: quinic acid, melittoside, phenylpropanoids and flavonoid derivatives. Specifically, two quinic acid derivatives along with two melittoside derivatives, two phenylethanoid glycosides ( $\beta$ -hydroxyverbascoside or  $\beta$ -hydroxyisoverbascoside is described for the first time in *Sideritis* species) and one flavonoid 7-O-diglycoside were identified along with six acetylated flavonoid 7-O-diglycosides of apigenin and isoscutellarein and four isomers of apigenin 7-O-(coumaroyl) glucopyranoside. Among the aforementioned compounds, the main constituents in the extract were found to be melittoside and quinic acid derivatives. Apigenin 7-O-acetylcoumaroyl - allosyl glucoside was identified and was characterised in the extract for the first time. Moreover, the chemical profile of *Sideritis raeseri* was found comparable with previous studied *Sideritis* species. Nine 7-O-allosyl glucosides of 5,8-dihydroxy substituted flavones were isolated from a fraction of the methanol extract of the aerial parts of *Sideritis raeseri* Boiss. & Heldr. subsp. *raeseri* (Gabrieli *et al.*, 2005), as well as with *Sideritis syriaca* (Kogiannou *et al.*, 2013)

Very recently, the metabolic profiling of six different *Sideritis* species growing in Greece (south Balkan peninsula): *Sideritis clandestina* subsp. *clandestina*, *Sideritis euboica*, *Sideritis perfoliata* subsp. *perfoliata*, *Sideritis raeseri* subsp. *raeseri*, *Sideritis scardica* and *Sideritis syriaca* (Papaefstathiou *et al.*, 2014) were compared (through HPTLC platform, and in LTQ Orbitrap HPLC-MS). The water extracts of the plants were found to contain the same secondary metabolites. Only limited quantitative differences were observed between them. In more details, the water extract of *Sideritis euboica* was similar to that of *Sideritis clandestina*, *Sideritis scardica*, *Sideritis raeseri* and *Sideritis perfoliata*. In contrary, *Sideritis syriaca* presented significant quantitative differences (only quantitative) with all previous referred

*Sideritis* species. Similar results were obtained when comparing the chemical profiles of all ethanol extracts (15%, 30% and 70%) of the six selected *Sideritis* species. Phytochemical investigation led to the isolation of the major components which were identified and structurally determined as acteoside, martynoside, and glycosides of apigenin, hypolaetin, isoscutelarein, 4'-*O*-methylisoscutelarein and 4'-*O*-methyl-hypolaetin. Moreover, the total phenol content was in the range of 82-140 mg GAE/g of extract (Papaefstathiou *et al.*, 2014)

### **Essential oil of *Sideritis* species**

The essential oil of *Sideritis scardica* (0.03%) contained mainly of  $\beta$ -pinene (17.9%); carvacrol (14.8%) and  $\alpha$ -pinene (Fraga, 2012); while another study (Kostadinova *et al.*, 2007) reported that the essential oils of the species *Sideritis scardica* and *Sideritis raeseri* from Bulgaria and FYROM consisted of diterpenes. The oil of *Sideritis raeseri* has higher concentrations of sesquiterpenes and as main components germacrone (25%) and elemol acetate (15.9%) (Bankova *et al.*, 1996; Bruno *et al.*, 2005, both cited in Kostadinova *et al.*, 2007; Bojovic *et al.*, 2011).

- Herbal preparation(s)

The monograph describes the uses of the comminuted herbal substance.

This monograph refers to *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L.

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

Search terms: *Sideritis*; *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L.; Mountain tea, *Sideritis herba*

Databases: Pubmed, Medline, HealLink, Scopus.

Libraries: University of Athens, Laboratory of Pharmacognosy and Chemistry of Natural Products of the National and Kapodistrian University of Athens.

Two comprehensive literature searches having been performed for the present assessment report used the search-term '*Sideritis scardica*' in the following toxicological databases:

- Medline, Pascal, Toxcenter, Biosis, Napralert and Toxline

## **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**

There are no registered or authorised medicinal products in the EU / EEA Member States

#### **Information on medicinal products marketed in the EU/EEA**

No registered medicinal products in the EU/EEA

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**

No combination medicinal products containing *Sideritis* are marketed in the EU

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

### Use in Albania

There are 4 *Sideritis* species used in Albania; (*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L.). *Sideritis scardica* is used in Albania traditionally as tea (bulk ware) and in recent times by modern tea packages as single portion (commercial product: 1-1.5 g/cup water 150 ml; <http://www.ndoj.it/www.alcaj.eu>)

A medicinal-ethnobotanical study in Albania confirmed the marketing as bulk ware in local markets as well pharmaceutical stores. Main use is the abdominal pain (stomach ache) and against sore throat by viral infections (Rexhepi *et al.*, 2013). Because wild collection of the raw material is dominant, the species *Sideritis scardica* as well *Sideritis raiseri* are often used parallel. It is used in Albanian folk medicine as a relaxant, during bronchitis and bronchial asthma, against colds and lung emphysema (UNDP report 2006 - Caji I malit).

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

*Sideritis* species are belonging to a large genus in the family of Labiatae. The genus (species not specified) was known to ancient Greeks, also from Theophrastus. Although Dioscorides in *De Materia Medica* describes three *Sideritis* species, only one (probably *Sideritis scordioides*) is thought to be related to *Sideritis* botanical genus. In ancient times *Sideritis* was a generic reference for plants capable of healing wounds caused by iron weapons during battles.

The name '*Sideritis*' (ironwort) derives from the Greek word for iron, 'σίδηρος' (SEE-thee-ros) literally translated as 'he who is or has the iron', because *Sideritis* was considered a great 'remedy against trauma from iron weapons,' that is to say wounds of war in ancient times. Dioscorides advises the herbal infusion of 'mountain tea' to soldiers as a rejuvenating, regenerating aid to help them heal quicker and fuller (González-Burgos *et al.*, 2011).

The *Sideritis* teas are named in a variety of ways, but they are commonly known as 'mountain tea' because some species grow in the high mountain areas (Bojovic *et al.*, 2011). In Crete, under the Venetian rule, *Sideritis* - ironwort (known today as *Sideritis syriaca*) gained another name, popular to this day on the island and throughout the world: *malotira* (μαλοτήρα). This name derives from the Italian: *male* means ailment/illness, while *tirare* means to pull, to draw out. Hence, *malotira* means draw out the illness. As Crete, almost every region of Greece has its own name for 'mountain tea', such as 'Olympos tea,' and 'Parnassos tea,' reflecting the name of the mountains where the *Sideritis* species of the region grows (Goliaris, 1998).

The most common English name other than mountain tea is 'Shepherd's Tea,' because Greek shepherds would use *Sideritis* species to make a brewed tea while tending their flocks high in the hills. Indeed, *Sideritis* (*malotira*) species are pleasant herbal remedies for a sore throat, a great aid in any disease of the respiratory system, possessing soothing and healing properties, as well as a healing cure for ailments of the digestive tract (Todorova & Trendafilova, 2014).

### Parts used

Apices of the stems are being used along with leaves and blossoms (*Sideritis scardicae herba*). The blooming stems are gathered during blossoming season in the months of June, July, August and

September. The tea is dried at shadow in sprigs by 7-8 pieces in a branch (Petkov, 1982; Jordanov, 1989; Stoyanov, 1973; Ganchev, 1995; Nikolov, 2006 all cited by Yaneva & Balabanski, 2013).

### History of the use

*Sideritis scardica* Griseb.

Very popular in Greece, Bulgaria, Albania and Republic of Macedonia; the plant is used either for the preparation of herbal teas, or for its aromatic properties in local cuisines. The herbal tea is commonly prepared by decoction, by boiling the stems, leaves and flowers in a pot of water, then often serving with honey and lemon. Mountain tea has been traditionally used to aid digestion, strengthen the immune system and suppress common cold, the flu and other viruses, allergies and shortness of breath, sinus congestion, even pain and mild anxiety. Research done on mountain tea supports its use to prevent colds, flu, and allergies. Most of this research has taken place in Universities in Greece, Turkey, FYROM, Bulgaria, and Albania, where the plants are indigenous (Yaneva & Balabanski, 2013).

**Other names:** Various names have been attributed to the plant in the ancient world, among them the names (Todorova & Trendafilova, 2014; Govaerts 2003 cited in Feistel, 2013):

- *Sideritis scardica* Griseb. - Internationally accepted name (PlantList, 2014). Commonly known as 'Mountain tea', 'Greek Mountain tea' and 'Olympus tea' however different regions linked to different species.
- Greece: Ελληνικό Τσάι του βουνού (Greek mountain tea), 'Olympus tea'
- Albania: Çaj Mali
- Bulgaria: Mursalski Tee, Pirinski Tee or 'Alibotushkitea'
- FYROM: Планински чај (Planinski Tea), 'Sharpla-ninsi chaj'
- England/UK: Greek Mountain Shephard's Tea
- Austria: Griechischer Bergtee
- Germany: Griechischer Bergtee (Greek Mountain tea), Griechisches Eisenkraut (Greek ironwort)
- Russia: Железница (Greek ironwort)

In a recently published review the perennial herbaceous plant *Sideritis scardica* Griseb. (syn= *Sideritis florida* Boiss. & Heldr., *Sideritis raeseri* subsp. *florida* (Boiss. & Heldr.) Papan & Kokkini, *Sideritis scardica* subsp. *longibracteata* Papan. & Kokkini) has been qualified as an endemic species of the Balkan Peninsula traditionally used as a healing aromatic herbal tea in the traditional medicine of the Balkan countries. In the traditional medicine 'Mountain tea' has been used mainly for the therapy of lung diseases like cough of different origin, asthma, lung emphysema and bronchitis. Furthermore, it is reported that *Sideritis scardica* is traditionally helpful for the treatment of inflammation, gastrointestinal disorders, and common cold and as dietary supplement for the prevention of anaemia (Đorđević *et al.*, 1993 cited in Todorova & Trendafilova, 2014). The author Alikovski, cited in this overview reported about treatment of the prostate urinary problems, angina pectoris, sore throat, and enhancement of diuresis as well as of the elimination of kidney gravel when the tea of this species is used. It has also been described that 'Pirin tea' was used together with other herbs as anti-rheumatic and immune stimulating agents. The tea is prepared from the aerial parts of the plant by infusion or decoction.

In written documents the use of *Sideritis scardica* in Bulgaria as a herbal tea and in the traditional medicine was pointed out. In written sources dated from the first decades of the last century in

Bulgaria 'Pirin mountain tea' in the folk medicine was recommended as tea that is 'aromatic and healing' in the treatment of respiratory diseases; in cough, asthma, bronchitis and for favourable effects on the respiratory organs (Karamitrev, 1934 cited in Yaneva & Balabanski 2013); in common cold (Jordanov, 1989 cited in Yaneva & Balabanski 2013); it helps to relieve symptoms of cough, bronchitis, common cold, sputum expectoration; cough of different origin (bronchitis, emphysema) (Stoyanov, 1973 cited in Yaneva & Balabanski 2013); for alleviation of asthma and chronic respiratory diseases; remedy that suppress coughing and get rid of excess mucus (Jordanov, 1989 cited in Yaneva & Balabanski, 2013). Infusions of aerial parts of *Sideritis scardica* are used in Bulgaria traditionally as expectorant for the treatment of pulmonary emphysema and angina pectoris (Ivancheva & Stantcheva, 2000 cited in Gonzalez -Burgos *et al.*, 2011). The aerial parts of 'mountain tea' are traditionally known for their anti-inflammatory, anti-microbial, and gastro-protective properties (Ðorðeviæ *et al.*, 1993 cited in Bojovic *et al.*, 2011; in Yaneva & Balabanski, 2013).

In addition to the traditional use as tea the species *Sideritis scardica* ethanolic extracts are topically administered as antiseptic after tooth extraction and for oral sores and crushed leaves with oil for the use as a poultice (Todorova & Trendafilova, 2014).

All biological activities previously cited in the literature have been mainly attributed to the phenolic and terpenoid content of this plant (Petreska *et al.*, 2011a & 2011b; Bojovic *et al.*, 2011).

*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., in Greece

- Mountain Tea is popular in Greece. It is in use for colds, respiratory problems and digestion. It is also used as an anti-inflammatory and to reduce fever.
- In Greece, it is sold in bulk in pharmacies, herb-and-spice shops, or it can be picked fresh and dried at home. Outside Greece, it is sold as 'Greek Mountain Tea,' or 'Greek Mountain Shepherd's Tea,' at specialty shops.

### Information on period of medicinal use in the European Union

*Sideritis* herba is very popular in Greece, and Bulgaria, the plant is used as a herb for the preparation of herbal teas. The herbal tea is commonly prepared by decoction, by boiling the stems, leaves and flowers in a pot of water, then often serving with honey and lemon. Mountain tea has been traditionally used to aid digestion, strengthen the immune system and suppress common cold, the flu and other viruses, allergies and shortness of breath, sinus congestion, even pain and mild anxiety (Alikowski, 2008; Floca *et al.*, 1981 cited in Raptou, 2011; Aneva, 2013; Yaneva & Balabanski, 2013).

### Use in Greece

*Sideritis syriaca*, *Sideritis scardica*, *Sideritis raeseri* and *Sideritis clandestina* are in use since ancient times as tea; these plants are used as a herb either for the preparation of herbal tea prepared by decoction, by boiling the stems, leaves and flowers in a pot of water. 15-25 g of the dried leaves and flowers /approx. 1 liter of boiling water (rd. 0.95 liter) (Floca *et al.*, 1981 cited in Raptou, 2011).

*Sideritis* species in Greece, are sold in bulk in pharmacies, herb-and-spice shops, or it can be picked fresh and dried at home. The popularity in Greece leads constantly increasing the area for cultivation (Goliaris, 1998) of *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr. and *Sideritis syriaca* L. (Feistel, 2013).

The mountain tea in Greece (mainly *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., and other only wild-growing *Sideritis* species) are used against stomach complaints, as tonic, as diuretic and as detoxification agent. The

decoction of the aerial parts has been used of colds and infections of the upper respiratory system and for digestion. In combination with cinnamon and honey properties that are enhanced. Even considered good as respiratory, as anti-irritant and as anti-anaemic because its iron content (Floca *et al.*, 1981 cited in Raptou, 2011).

### Use in Bulgaria

It was reported by Aneva that four species of *Sideritis* herba are endemic according to Flora Republic of Bulgaria 1989 (*Sideritis lanata*, *Sideritis montana*, *Sideritis syriaca*, and *Sideritis scardica*). For *Sideritis scardica* the traditional use as herbal medicine is described is a mucus-reducing and soothing agent for coughs and bronchitis (Aneva, 2013).

Stoyanov delivered in 1960 the first written source about the use of three *Sideritis* species (*Sideritis montana*, *Sideritis taurica* and *Sideritis scardica*) as tea. Tea was mainly sold as bulk ware in special food shops/herbal shops near the origin area of growing or in pharmacies. Aneva described the traditional use of *Sideritis scardica* in Bulgaria in detail. 'Tea of longevity' is the name in the Rhodopoe mountain. Decoctions or infusions of the aerial part are used as antioxidant, anti-inflammatory, anti-microbial, vulberary, analgesic, caminative and anti-ulcerative agents (Aneva, 2013).

Tea from *Sideritis scardica* used since ancient times to combat the negative effects of asthma and bronchitis, and as a cough suppressant (Davidov *et al.*, 1939; summarised in Todorova and Trendafilova, 2014).

It is reported that 'Mursalski Tea' is also appropriate for treating chronic kidney disease. According to the authors, the tea causes a change of pH in the urine, it enhances diuresis and contributes to the destruction and elimination of kidney gravel (Alikowski, 2008).

Todorova & Trendafilova (2014) describes that the herbal tea is recommended to be used by infusing it with boiling water for 20 to 30 minutes, without continuous simmering. After filtering, the tea can be consumed hot or cold throughout the day.

Three to five flowering stems (approx. 4 g each - 12-20 g) are necessary for one liter of tea. The large range in traditional dosage goes back to the use of raw material in bulk, means small bouquets on flowering stems (Stoyanov, 1973 cited in Yaneva & Balabanski 2013).

Infusion: 3-4 sprigs are cut and 2 cups of boiling water (300-400 ml) are added. After 10 minutes the infusion is drained and 1 table spoon is taken every 2 hours. Always it should be drunk as warm tea in colds (Stoyanov, 1973 cited in Yaneva & Balabanski 2013).

Decoction: 3 table spoons of the herb are boiled in 1 l water for 3 minutes. One glass of wine of the decoction is drunk up to 3 times daily, instead of water before meal. (Ivanov *et al.*, 1977 cited in Yaneva & Balabanski, 2013).

Infusion 3–4 g, soaked in 200 g hot water, sweetened with sugar and to be drunk as tea several times (2-3 times) daily (Bojchinov, 1943 cited in Yaneva & Balabanski, 2013).

The plant Pirin tea (*Sideritis scardica* Griseb.) has been placed in the List of medicinal plants (herbs index) that is regulated under the Medicinal Plants Act, published in State Gazette, No. 29 as of April 7, 2000 in Bulgaria cited in Yaneva & Balabanski, 2013.

The main effects that characterise *Sideritis scardica* in different diseases are: expectorant, alleviating in inflamed mucous membranes of the respiratory system, antitussive, anti-inflammatory (in diseases of the respiratory system and rheumatism); anti-asthmatic (Yaneva & Balabanski, 2013).

Different tea applications as 'Greek mountain tea' are on the market as bulk ware for cough and colds are also marketed in Germany. According to the overview of the European market, there are no registered/authorised herbal preparations containing Sideritis on the market. However according to references listed below, in the Balkan peninsula (Greece, Turkey, Bulgaria, Albania; Serbia, FYROM , etc.) Sideritis herba is widely in medicinal use for at least 40 years (in accordance with existing references).

Therefore for Sideritis herba a period of at least 30 years of medicinal use, as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled. The evidence on traditional medicinal use is confirmed by a large number of publications providing consistent information.

The monograph describes the use of the comminuted herbal substance as a herbal tea (infusion, decoction) for oral use.

**Table 1:** Overview of historical data

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
<i>Sideritis scardica</i> herba	expectorant, alleviating in inflamed mucous membranes of the respiratory system, antitussive, sweat reducing	<u>Infusion</u> - 3-4 g, soaked in 200 g hot water to be drunk as tea, (proposed up to 2-3 times)	Bojchinov, 1943 cited in Yaneva & Balabanski 2013
<i>S. montana</i> , <i>S. taurica</i> <i>S. scardica</i> ; <i>S. raeseri</i> ; <i>S. syriaca</i>	For relief of cough associated with cold	3-4 of sprigs are cut and 2 cups of boiling water (300-400 ml) are added. After 10 minutes the infusion is drained and 1 table spoon is taken every 2 hours. Always it should be drunk as warm tea in separate sips	Ivanov <i>et al.</i> , 1977 cited in Yaneva & Balabanski 2013 Stoyanov, 1973 cited in Yaneva & Balabanski 2013 Davidov <i>et al.</i> , 1939; summarised in Todorova & Trendafilova 2014 Alikowski, 2008 Todorova & Trendafilova, 2014
<i>S. syriaca</i> , <i>S. scardica</i> , <i>S. raeseri</i> and <i>S. Clandestina</i> , herba	colds, respiratory problems, digestion, coughs and gastrointestinal disorders	<u>Infusion</u> - 15-25 g of the dried leaves and flowers /approx. 1 liter of boiling water (rd. 0.95 liter) [2.3-4 g / 150 ml of hot water]	Goliaris, 1998 Floca <i>et al.</i> , 1981 cited in Raptou, 2011
<i>Sideritis scardica</i> herba	relieve symptoms of cough, bronchitis, common cold, sputum expectoration; cough of different origin (bronchitis, emphysema)	<u>Infusion</u> - 2-5 g of the dried leaves and flowers in 200 ml (1 cup) of hot water, to be left for 5-10 min and then to be drunk up to 3-4 - time per day	Karamitrev, 1934 cited in Yaneva & Balabanski, 2013 Jordanov, 1989 cited in Yaneva & Balabanski, 2013 Đorđević <i>et al.</i> , 1993 cited in Bojovic <i>et al.</i> , 2011 and Todorova & Trendafilova, 2014

### **2.3. Overall conclusions on medicinal use**

*Sideritis scardica* Griseb.; *Sideritis clandestine* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr. and *Sideritis syriaca* L. were included in the monograph, because evidence on the period of traditional use (30 years safe use including 15 years in the EU) with well-defined posologies and mode of preparation exist for these four *Sideritis* species.

#### **The indications recommended in the monograph:**

1. Traditional herbal medicinal product used for the relief of cough associated with cold.
2. Traditional herbal medicinal product used for the relief of mild gastrointestinal disorders.

#### **Posology**

*Adults and elderly*

##### **Indication 1) and 2)**

Single dose

Herbal tea: 2-4 g of the comminuted herbal substance in 150 ml-200 ml of boiling water as a herbal infusion, 2-3 times daily.

Daily dose: up to 12 g

The use in children and adolescents under 18 years of age is not recommended.

#### **Duration of use**

##### **Indication 1)**

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.

##### **Indication 2)**

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

**Table 2:** Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
<i>S. syriaca</i> , <i>S. scardica</i> , <i>S. raeseri</i> and <i>S. clandestina</i>	colds, respiratory problems, digestion	<u>Infusion</u> 15-25 g of the dried leaves and flowers /approx. 1 liter of boiling water (rd. 0.95 liter) 15-25 g of the dried leaves and flowers /approx. 1 liter of boiling water (rd. 0.95 liter)  2.25-3.75 150 ml	Goliaris, 1998 Floca <i>et al.</i> , 1981 cited in Raptou, 2011
<i>Sideritis scardica</i> herba	expectorant, alleviating in inflamed mucous membranes of the respiratory system  relieve symptoms of cough associated with common cold	<u>Infusion</u> - 3-4 g, soaked in 200 g hot water to be drunk as tea, to be drunk as tea, several times daily (proposed up to 2-3 times) 2-5 g of the dried leaves and flowers in 200 ml (1 cup) of hot water, to be left for 5-10 min and then to be drunk up to 3-4- time per day	Bojchinov, 1943 cited in Yaneva & Balabanski 2013  Karamitrev, <u>1934</u> in Yaneva & Balabanski 2013 Jordanov, <u>1989</u> , Yaneva & Balabanski 2013 Đorđević <i>et al.</i> , 1993 cited in both Bojovic <i>et</i> <i>al.</i> 2011; Todorova & Trendafilova, 2014

## 3. Non-Clinical Data

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

#### 3.1.1. Primary pharmacodynamics

##### In vitro experiments

##### Antimicrobial activity

A recent review publication summarises the data of the antimicrobial activity of *Sideritis scardica* (ethanol extract and its ethyl-ether, ethyl-acetate, and *n*-butanol fractions) (Tadić *et al.*, 2007 cited in Todorova & Trendafilova, 2014). Antimicrobial activity of varying degrees against *Staphylococcus epidermidis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and yeast *Candida albicans* has been demonstrated. Maximum activity was observed against *S. epidermidis*, *M. luteus*, *E. coli* and *P. aeruginosa*, moderate activity against *K. pneumoniae*. The *n*-butanol fraction was the most active (50 mg/ml ethanol solution exhibited 206.7% of ampicillin activity against *S. epidermidis*).

*Sideritis scardica* Griseb. has been investigated also for its antimicrobial properties against Gram-positive bacteria, *Streptococcus pyogenes*, *Streptococcus canis*, *Moraxella catarrhalis*, *Staphylococcus aureus*, methicillin resistant *Staphylococcus aureus*, *Corynebacterium pseudotuberculosis*, *Enterococcus faecalis*, Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Pasteurella multocida* and *Haemophilus sp.*, and yeast *Candida albicans*. The minimal inhibitory concentration (MIC) values of the extracts tested ranged from 40 to 2.56 µg/ml. The investigators concluded that the different types of terpenoids could contribute for this antibacterial activity (Tadić *et al.*, 2012 cited in Todorova & Trendafilova).

Extracts from *Sideritis scardica*, *Sideritis syriaca* and *Sideritis montana* (extracted with organic solutions) showed an activity against *Staphylococcus aureus*, and butanol extract of *Sideritis syriaca* exhibited anti-yeast activity against *C. albicans* (Yaneva & Balabanski, 2013).

##### Spasmolytic activity

In a study, the effects of an ethanol extract of *Sideritis raeseri* on intestinal activity were investigated. Air-dried and powdered aerial parts were extracted with 96% ethanol. The rat ileum preparations were incubated in Tyrode's solution gassed (95% O<sub>2</sub>/5% CO<sub>2</sub>) at 37°C. The ethanol extract of *Sideritis raeseri* (0.03-0.3 mg/ml) relaxed spontaneous contractions in isolated rat ileum, similar to that produced by papaverine. The plant extract in a concentration-dependent manner (0.015-0.15 mg/ml) significantly inhibited the contractile response to acetylcholine (p<0.01). A relaxation-inducing effect of *Sideritis raeseri* extract was observed on the pre-contracted ileum by histamine and barium chloride. The plant extract (0.03-0.3 mg/ml) significantly shifted the histamine concentration-response curve to the right and down (p<0.01). The *Sideritis raeseri* extract (0.03-0.3 mg/ml) significantly inhibited the contractions induced by barium chloride (p<0.01). According to the authors, the results showed that the ethanol extract of *Sideritis raeseri* can produce inhibition of the spontaneous rat ileum contractions and contractions induced by different spasmogens. According to the authors these data indicated that *Sideritis raeseri* acts as a spasmolytic on intestinal smooth muscle, which supports its use in gastrointestinal disorders (Brankovic *et al.*, 2011).

## ***In vivo experiments***

### **Anxiolytic-like and antioxidant properties**

Another study monitored the effect of drinking of herbal tea from *Sideritis clandestina* for 6 weeks on behavioral and oxidant/antioxidant parameters of adult male mice and also to evaluate its phytochemical composition.

The phytochemical profile of the *Sideritis* tea was determined by LC-UV diode array coupled to ion-trap mass spectrometry with electrospray ionisation interface. The effects of two doses of the herbal infusion (2 and 4% w/v, daily) intake on anxiety-like state in mice were studied by the assessment of their thigmotactic behavior. The oxidant/antioxidant status of brain (-Ce), liver and heart of adult male Balb-c mice following the consumption of *Sideritis* tea was also evaluated via the measurement of malondialdehyde (MDA) and reduced glutathione (GSH) levels using fluorometric assays. The study was further extended to determine the antioxidant effects of the herbal tea on specific brain regions (cerebral cortex, cerebellum and midbrain). The identified compounds were classified into several natural product classes: quinic acid derivatives, iridoids, phenylethanol glycosides and flavonoids. The results showed that only the 4% *Sideritis* tea exhibited anxiolytic-like properties as evidenced by statistically significant ( $p < 0.05$ ) decrease in the thigmotaxis time and increase in the number of entries to the central zone in comparison with the control group. Intake of both tea doses (2 and 4% w/v) resulted in elevated GSH (12 and 28%, respectively,  $p < 0.05$ ) and decreased MDA (16 and 29%,  $p < 0.05$ ) levels in brain (-Ce), while liver and heart remained unaffected. Intake of herbal tea (2 and 4% w/v) caused a significant increase in GSH of cerebellum (13 and 36%, respectively,  $p < 0.05$ ) and midbrain (17 and 36%,  $p < 0.05$ ). Similarly, MDA levels were decreased in cerebellum (45 and 79%, respectively,  $p < 0.05$ ) and midbrain (50 and 63%, respectively,  $p < 0.05$ ), whereas cerebral cortex remained unaffected. The authors concluded that the water extract (infusion) of mountain tea drinking prevents anxiety-related behaviors and confers antioxidant protection to rodent's tissues in a region-specific in a dose-dependent manner (Vassilopoulou *et al.*, 2013)

### **Gastro protective and anti-inflammatory activities**

The ethanol, diethyl ether, ethyl acetate and *n*-butanol extracts of *Sideritis scardica* were tested for their anti-inflammatory and gastroprotective activities. The extracts were dissolved in DMSO, and administered *p. o.* in doses of 50–200 mg/kg 60 minutes prior to ethanol. Ranitidine given in doses of 5–20 mg/kg *p. o.* was used as a reference drug. Compared to the effect of the positive control, the anti-inflammatory drug indomethacin (4 mg/kg), which produced a 50% decrease in inflammation, diethyl ether and *n*-butanol extracts exhibited about the same effect in doses of 200 and 100 mg/kg (53.6 and 48.7%; 48.4 and 49.9%, respectively). All investigated extracts produced dose-dependent gastroprotective activity with the efficacy comparable to that of the reference drug ranitidine. The reduction of the rat paw oedema was reached by the doses of 100 and 200 mg/kg and the level was comparable to the positive control, indomethacin, which was administered in a dose of 4 mg/kg producing 50% reduction (Tadić *et al.*, 2012).

**Table 3:** Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
<i>Sideritis scardica</i>	Ethanol extracts	<i>in vitro</i>	Tadić et al., 2007 cited in Todorova & Trendafilova, 2014	Antimicrobial activity against <i>S. epidermidis</i> , <i>M. luteus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , moderate activity against <i>K. pneumonia</i> <i>n</i> -butanol fraction was the most active (50 mg/ml ethanol solution exhibited 206.7% of ampicillin activity against <i>S. epidermidis</i> )
<i>Sideritis syriaca</i>	Butanol extract	<i>in vitro</i>	Yaneva & Balabanski, 2013	Anti-yeast activity against <i>C. albicans</i>
<i>Sideritis scardica</i> ,	Ethanol and water extracts	<i>in vitro</i>	Tadić et al., 2012 cited in Todorova & Trendafilova, 2014	MIC values from 40 to 2.56 µg/ml <i>S. pyogenes</i> , <i>S. canis</i> , <i>M. catarrhalis</i> , <i>S. aureus</i> , methicillin resistant <i>S. aureus</i> , <i>C. pseudotuberculosis</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>P. multocida</i> , <i>Haemophilus sp.</i> , <i>C. albicans</i>
<i>Sideritis raeseri</i>	Ethanol extract	<i>in vitro</i> Rat ileum preparations were incubated in Tyrode's solution gassed (95% O <sub>2</sub> /5% CO <sub>2</sub> ) at 37°C	Brankovic et al., 2011	The ethanol extract of <i>Sideritis raeseri</i> (0.03-0.3 mg/ml) relaxed spontaneous contractions in isolated rat ileum, similar to that produced by papaverine
<i>Sideritis clandestina</i>	Water extracts (infusions drinkable)	<i>in vivo</i>	Vassilopoulou et al., 2013	4% <i>Sideritis</i> tea exhibited anxiolytic-like properties as evidenced by statistically significant (p<0.05) decrease in the thigmotaxis time and increase in the number of entries to the central zone in comparison with the control group

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
<i>Sideritis scardica</i>	Ethanol, diethyl ether, ethyl acetate and <i>n</i> -butanol extracts (50–200 mg/kg )	<i>in vivo</i> Gastroprotective activities on an ethanol-induced acute gastric damage in rats	Tadić <i>et al.</i> , 2012	All extracts produced dose-dependent gastroprotective activity with the efficacy comparable to that of the reference drug ranitidine (5–20 mg/kg).

### 3.1.2. Secondary pharmacodynamics

#### Antioxidant activity

Plant samples from several species and populations of the genus *Sideritis* grown in Bulgaria (*Sideritis scardica*, *Sideritis syriaca* and *Sideritis montana*) were tested for their antioxidant activities by the  $\beta$ -carotene bleaching test (BCBT), 2,2'-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method and static headspace gas chromatography (HS-GC) and compared with the antioxidant activity of two reference compounds of different polarity, butylated hydroxytoluene (BHT) and rosmarinic acid. The highest antioxidant activity in the BCBT, close to that of BHT, was observed for the more apolar extracts. The inhibitory effect on  $\beta$ -carotene bleaching of the polar extracts and rosmarinic acid was much lower than that of BHT. The inhibition of hexanal formation in bulk safflower oil by most *Sideritis syriaca* and *Sideritis scardica* extracts was as effective as BHT but less so than rosmarinic acid. Extracts from butanol and from ethyl acetate and the total methanol extracts from all *Sideritis* plants studied showed a strong radical scavenging activity against 2,2'-diphenyl-1-picrylhydrazyl, close to that of rosmarinic acid. *Sideritis montana* extracts were, as a whole, slightly weaker radical inhibitors than the extracts from the other two species (Koleva *et al.*, 2003).

In another study *Sideritis scardica*, was tested (Tadić *et al.*, 2012) (ethanol, diethyl ether, ethyl acetate and as *n*-butanol extracts) for their antioxidant activity and showed that the diethyl ether extract of *Sideritis scardica* revealed the highest anti-inflammatory effect.

In another *in vitro* study (Danesi *et al.*, 2013) the authors compared the antioxidant activity of *Sideritis scardica* to a *Camellia sinensis* extract as well as to the antioxidant  $\alpha$ -tocopherol in a biological system (HepG2 cells) against oxidative stress. The results did not show significant differences between the extracts. For *Sideritis scardica* the authors identified a lower phenolic concentration and a smaller total antioxidant capacity than the *Camellia sinensis* extract; however, cellular antioxidant effects in the test system were similar for both extracts.

The publication of Petreska and coworkers (Petreska *et al.*, 2011a) addresses the phytochemical evaluation and the related antioxidant activity as well as the dietary burden of phenolics by a cup of domestic infusion of *Sideritis*. It has been analysed that the total phenolic content for *Sideritis* was around 190 mg when a 2 g infusion bag was used in case of the methanol extracts, and it was about 72 mg in water extracts. As a result, the methanol extract of *Sideritis raeseri* (wild growing) demonstrated the highest antioxidant capacity as shown by DPPH, ABTS and FRAP assays and the antioxidant activity was linearly correlated with phenolic content.

In another study (Papaefstathiou *et al.*, 2014) the free radical scavenging (DPPH) were studied on six different *Sideritis* species growing in Greece (south Balkan peninsula): *Sideritis clandestina* subsp. *clandestina*, *Sideritis euboica*, *Sideritis perfoliata* subsp. *perfoliata*, *Sideritis raeseri* subsp. *raeseri*, *Sideritis scardica* and *Sideritis syriaca*. The scavenging assays revealed that all extracts possessed significant antioxidant activity (% inhibition >74 at 300  $\mu$ g/ml).

#### Antiglioma activity

Todorova & Trendafilova (2014) summarised the effects of *Sideritis scardica* extracts (ethanol, diethyl ether, ethyl acetate, and *n*-butanol) on C6 rat glioma cells. The extracts decreased the viability of the C6 rat glioma to 59.4% compared to the untreated cells. The viability of the rat primary astrocytes was not impacted negatively by the same extracts concentrations used (50  $\mu$ g/ml) but the cellular morphology and actin distribution were damaged. It has been reported that the four extracts increased the production of reactive oxygen species in C6 rat glioma cells, the rat primary astrocytes, as well as the caspase activation and subsequent apoptotic cell death. The diethyl ether and ethyl acetate

extracts caused cytotoxic effects on C6 rat glioma cells with IC<sup>50</sup> 81.6 µg/ml and 109.4 µg/ml, respectively. The main flavonoids like apigenin and luteolin were reported responsible for the cytotoxic effects on the C6 rat glioma cells. No cytotoxicity against rat astrocytes in primary culture was observed with the extracts.

Different extracts of the aerial parts of *Sideritis scardica* have been investigated on the reuptake of serotonin, dopamine and noradrenaline in rat brain synaptosomes. The *in vitro* study has been performed according to the method of Perovic and Müller, 1995 (Feistel, 2013). Together with [<sup>3</sup>H]-serotonin, [<sup>3</sup>H]-dopamine or [<sup>3</sup>H]-noradrenaline the rat synaptosomes were incubated with increasing concentrations of the extracts. As positive controls imipramine (serotonin), GBR 12909 (dopamine) and protriptyline (noradrenaline) have been implemented. At a dosage of 100 mg *Sideritis scardica* ethanolic extract/kg body weight similar spectral changes were observed compared to the *Rhodiola rosea* root extract in the same dosage. Main effects seen were a significant attenuation of alpha2 waves followed by decreases in spectral theta power in the frontal cortex and hippocampus. Similar spectral changes have been found after the administration of 1 mg/kg paroxetine, a synthetic anti-depressive drug and methylphenidate. The author suggested that *Sideritis scardica* might be regarded as an up to now unknown substitute of the class of adaptogens with possible psychostimulant and anti-depressive effects and might be in accordance with the findings of Knoerle (2012) who reported the inhibition of the re-uptake of serotonin, dopamine and noradrenaline. The authors concluded that the tested extracts of *Rhodiola* and *Sideritis* revealed similar frequency patterns comparable to a psychostimulant drug (methylphenidate) as well to the anti-depressive drug (paroxetine).

### **Cytotoxic activities**

Ethanol, diethyl ether, ethyl acetate and *n*-butanol extracts of *Sideritis scardica*, were tested for their cytotoxic potential (Tadić *et al.*, 2012). For the evaluation of cytotoxic potential of the different extracts PBMC, B16 melanoma, and HL-60 leukemic cells were used and compared to the cytotoxic activity of the main phenolic compounds of the extracts. Only diethyl ether extract caused significant dose-dependent cytotoxicity in B16 cells and HL-60 cells, decreased cell growth to 51.3% and 77.5% of control, respectively, when used at 100 µg/ml. The most cytotoxic compounds were luteolin, apigenin-7-O-β-glycoside, apigenin, and luteolin-7-O-β-glycoside.

### **Influence on memory**

Todorova and Trendafilova (2014) recently summarised the biological activity of *Sideritis scardica* Griseb. They presented the results of *Sideritis scardica* on memorising skills of mice in the Morris water maze experiment. The results revealed that the behavior testing of mice with Alzheimer's disease when treated with extract from *Sideritis scardica* compared to untreated mice showed a reduction of total α-amyloid amount by 55%.

### **Triple monoamine re-uptake inhibitors**

Knoerle (2012) demonstrated that water and alcoholic extracts of *Sideritis scardica* inhibited the serotonin, noradrenaline and dopamine uptake in rat brain synaptosomes and additionally the serotonin uptake in human JAR cells (placental choriocarcinoma cells). The uptake of all three monoamine was inhibited in a concentration-dependent manner. The alcoholic extracts were more effective than the water extract when tested in rat brain synaptosomes with EC<sub>50</sub> values of about 30–40 µg/ml. In case of the human serotonin transporter it has been shown that the methanol extract was more effective (EC<sub>50</sub> 1.4 µg/ml). The author suggested that among others, terpenes, flavonoids and phenols could be responsible for the effects on the CNS activity. They concluded that the tested *Sideritis scardica* extracts could be used for the prevention and treatment of anxiety disorders, major depression, attention-deficit hyperactivity disorder, mental impairment or neurodegenerative diseases.

### 3.1.3. Safety pharmacology

No data

### 3.1.4. Pharmacodynamic interactions

None reported

### 3.1.5. Conclusions

*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., have been described as endemic species of the Balkan. They are traditionally used as healing aromatic herbal teas in folk medicine of the Balkan countries since centuries mainly for the therapy of lung diseases like cough of different origin, asthma, lung emphysema and bronchitis. Furthermore, it is reported that *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., are helpful and supportive based on traditional knowledge for the relief of cough associated with cold, also used for relief of mild gastrointestinal disorders. Pharmacological properties of the plant found in relevant scientific literature like the anti-microbial activities make the traditional use in uncomplicated disorders of the lung plausible.

The published data referring to the indications and preparations are limited, but existing data on the above-mentioned pharmacological activities support the plausibility of the traditional use of *Sideritis* herba, for relief of cough associated with cold. Moreover the traditional use of the plant against gastrointestinal disorders is considered plausible based on the results (anti-inflammatory, gastro protective) from an *in vivo* study (Tadić *et al.*, 2012). The data indicate that *Sideritis* species act as spasmolytic on intestinal smooth muscle, which supports their use in gastrointestinal disorders (Brankovic *et al.*, 2011).

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

By *in vivo* studies, several phenolics belonging to *Sideritis* species like flavones and hydroxycinnamic acids have been studied with regards to their absorption and metabolisation by the human gastrointestinal tract and following occurrence at systemic level in plasma and excretion by urine (Meyer *et al.*, 2006; Lafay *et al.*, 2008; Jia *et al.*, 2009, all cited in Petreska *et al.*, 2011a).

Based on *in vivo* experiments with animals and clinical trials with humans, it can be concluded that the flavones apigenin, luteolin and scutellarein are absorbed but at low rate (around 0.25% of the initial intake). They are extensively conjugated to glucuronides, sulphates and transformed to methylated forms (Meyer *et al.*, 2006; Lafay *et al.*, 2008; Jia *et al.*, 2009; Hanske *et al.*, 2009, all cited in Petreska *et al.*, 2011a). 3-caffeoylquinic acid and 5-caffeoylquinic acid are assumed to be directly absorbed in the stomach, hydrolysed by enterocytes at the small intestine and absorbed by the caecal microflora as caffeic acid (Lafay *et al.*, 2006 and Lafay *et al.*, 2008, both cited in Petreska *et al.*, 2011a). The authors' summarised that the most abundant phenolics by domestic infusion (boiling water) were esterified forms of flavones and hydroxycinnamic acids and the preparation of a tea should consist of 60% of leaf and 40% of flower, decreasing up to the maximum the addition of stem (Petreska *et al.*, 2011a).

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

No toxicology studies could be retrieved from the literature. However, unpublished data were provided to the HMPC during the call for scientific data by Finzelberg GmbH & Co. KG.

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

A *Sideritis* herb dry extract (70% native, 30% maltodextrin; extraction solvent: 20% V/V ethanol), has been tested in an acute oral toxicity study in Sprague Dawley rats (Bhide, 2011a). The study has been performed according to the OECD guideline for the Testing of Chemicals<sup>1</sup>. No gross or histopathological abnormalities and no signs of toxicity or mortality could be detected in all six female rats throughout the study period of 14 days when treated at the dose level of 2000 mg/kg of the test item. The tested *Sideritis* herb extract has been assigned to category 5 covering the range for oral LD<sub>50</sub> to be 2000 mg/kg-5000 mg/kg body weight.

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

A *Sideritis scardica* herb dry extract (70% native, 30% maltodextrin; extraction solvent: 20% V/V ethanol), has been tested in a repeated dose 28 day oral toxicity study in Sprague Dawley rats followed by a 14 day recovery period (Bhide, 2011b). The study has been performed according to the OECD guideline for testing chemicals No. 407, 'Repeated dose 28 day oral toxicity study in rodents' adopted on 3<sup>rd</sup> October 2008. The aim of the study was the investigation of the toxicological properties of the *Sideritis* herb extract on the target organ toxicity, and the 'No Observed Adverse Effect Level (NOAEL) in rats (30 males and 30 females distributed to 6 groups with 5 rats/sex/group) after repeated oral administration during the study period of 28 days. The assayed extract, having been suspended in distilled water, was administered by gavage to animals at dosages of 250 mg/kg, 500 mg/kg and 1000 mg/kg body weight and compared to the control groups having received distilled water only. Additionally, doses of 0 mg/kg and 1000 mg/kg were used to investigate the reversibility of possible delayed occurrence of symptoms.

All rats survived the study period, the body weight did not change, the food intake was comparable in all groups, and that no signs of toxicity could be found during the period of 28 days and the recovery period of 14 days. Furthermore, towards the end of exposure period the sensory reactivity of auditory, visual and proprioceptive stimuli did not show abnormalities in the treatment and control group. Hematological analysis revealed also no abnormalities except for an increase of the MCV and MCHC values at the dose of 1000 mg/kg in male and in case of platelets at 1000 mg/kg in female rat. A statistically significant decrease was documented for the values of total WBC at the dose of 500 mg/kg, male) and MCHC (500 mg/kg, female) in male and female rats treated with different doses of the test item; however, the changes were only marginal. No hematological changes have been caused by the *Sideritis* extract, except of a decrease of MCH in female animals from 1000 mg/kg reversal group sacrificed on day 43 but estimated to be in the biological range. Concerning the clinical biochemical parameters of Calcium and sodium (250 mg/kg, 500 mg/kg and 1000 mg/kg, male), Chloride (250 g/kg and 1000 mg/kg, female) and Sodium (500 mg/kg and 100 mg/kg, female) have been marginally influenced by the test item. The organ weight of the tested rats from different dose and control groups as well as from that of the reversal group (1000 mg/kg) did not differ. Moreover, the pathological and histopathological examinations did not indicate any abnormalities which could be referred to the treatment with the *Sideritis scardica* dry extract.

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<sup>1</sup> (No. 423, Section 4: Health Effects) "Acute Oral Toxicity- Acute Toxic Class Method "Adopted on 17th December 2001.

In conclusion, the authors determined the NOAEL of the *Sideritis scardica* dry extract to be 1000 mg/kg body weight in male and female animals when the Sprague Dawley rats were treated over a time period of 28 days in this repeated dose oral toxicity study.

### 3.3.3. Genotoxicity

According to the 'Guideline on Selection of Test Materials for Genotoxicity Testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products' the genotoxicity tests for the *Sideritis scardica* dry extract have been carried out in line with bracketing/matrixing-model (EMA/HMPC/67644/2009). Four Ames tests with the dry extracts from *Sideritis scardica* herb of different polarity (water; 20% (V/V) ethanol; 50% (V/V) ethanol; *n*-heptane) have been evaluated for their genotoxic potential [These extracts cover the entire spectrum of phytochemical constituents of the *Sideritis scardica* herb, including polar and non-polar constituents. For the monograph only the results obtained with the water extract are of interest

Four Ames tests with different polarity:

The dry extract of *Sideritis* (70% native, 30% maltodextrin; DER native: 4-8:1; extraction solvent water) was examined in the 5 *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 according to the plate incorporation test, each carried out without and with metabolic activation (BSL Bioservice, 2011a). The first experiment was carried out as a plate incorporation test and the second as a pre-incubation test. In the experiment I the following concentrations of 31.6, 100, 316, 1000, 2500 and 5000 µg/plate and in the experiment II 250, 500, 1000, 2000, 3000, 4000 and 5000 µg/plate (only for TA 98 without metabolic activation) have been tested. For clarification of the results of tester strain TA100 in experiment I and II a third incorporation test was performed (only for TA 98 without metabolic activation) with the concentrations of 500, 1000, 2000, 3000, 4000 and 5000 µg/plate. As a result, in all tester strains of I and II precipitation was found and additionally in experiment III at a dose of 5000 µg/plate. No toxic effects have been observed under the test conditions. No increase in revertant colony numbers of any of the five tester strains have been observed in the presence or absence of metabolic activations in all experiments. In summary, the *Sideritis* extract herb aquos. sicc. did not cause gene mutations by base pair changes or frameshifts in the genome of the tester strains used and therefore, the test item has been considered not to be mutagenic.

The dry extracts of *Sideritis* (70% native, 30% maltodextrin; extraction solvent 20% (V/V) ethanol); (70% native, 15% maltodextrin, 15% silica; DER native: 6:1; extraction solvent 50% (V/V) ethanol and 50% native, 50% silica; DER native: 83:1; extraction solvent heptane) have been tested in the *Salmonella typhimurium* strains TA 97a, TA 98, TA 100, TA 1535 and TA 102 with and without metabolic activation (BSL Bioservice, 2011b; BSL Bioservice, 2014a; BSL Bioservice, 2014b). These results are not of interest as only the water extracts are included as herbal preparations in the proposed monograph.

### 3.3.4. Carcinogenicity

No carcinogenicity studies carried out on mountain tea herb in the scientific literature.

### 3.3.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies carried out on mountain tea herb was found in the scientific literature.

The safety of mountain tea herb during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

### 3.3.6. Local tolerance

No data available.

### 3.3.7. Other special studies

No data available.

### 3.3.8. Conclusions

No toxicology studies could be retrieved from the literature. However, unpublished data were provided to the HMPC during the call for scientific data by Finzelberg GmbH & Co. KG. The toxicological data such as a single dose and a repeated dose study were summarised and presented. In the acute oral toxicity study a *Sideritis* herb extract, sicc. (70% native, 30% maltodextrin; extraction solvent: 20% V/V ethanol) no histopathological abnormalities and no signs of toxicity or mortality could be detected in rats when treated at the dose level of 2000 mg/kg. The tested *Sideritis* herb extract has been assigned to category 5 covering the range for oral LD<sub>50</sub> to be 2000 mg/kg- 5000 mg/kg body weight. The same extract has been tested in a repeated dose 28 day oral toxicity study in rats followed by a 14 day recovery period. No mortality and no changes in body/organs weight or food consumption have been observed and the NOAEL of the *Sideritis scardica* dry extract has been determined to be 1000 mg/kg body weight.

According to the 'Guideline on Selection of Test Materials for Genotoxicity Testing for Traditional Herbal Medicinal Products/Herbal Medicinal Products' (EMA/HMPC/67644/2009) the genotoxicity tests have been carried out in line with bracketing/matrixing-model. Four Ames-tests with dry extracts from *Sideritis scardica* herb of different polarity (water; 20% (V/V) ethanol; 50% (V/V) ethanol; *n*-heptane) have been conducted and thus, the entire spectrum of polar and non-polar constituents of *Sideritis scardica* herb was considered. The four Ames-tests were negative in all test concentrations. The Ames-tests were conducted according to GLP and in line with ICH guidelines. The tests were suitable to evaluate the genotoxicity of *Sideritis scardica* Griseb. herb extracts and the results were unequivocally negative. For the analysis of the mutagenic potential the water extract of *Sideritis scardica* was tested covering the proposed herbal preparation of the monograph. In none of the Ames tests a clear and dose related increase in the number of revertants occurred and/or no biologically relevant positive response for at least one of the dose groups occurs in at least one tester strain with or without metabolic activation; therefore *Sideritis scardica* is not considered to be mutagenic.

The available toxicological data and the results of the Ames-tests performed according to the bracketing/matrixing-model support the positive safety profile of *Sideritis scardica*.

## 3.4. Overall conclusions on non-clinical data

*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., are botanically very closely related species of the same genus. Pharmacological properties of *Sideritis* species found in relevant scientific literature, like the anti-inflammatory and anti-microbial activities, supports the traditional use in relief of cough associated with cold. Moreover, the traditional use of the plant against gastrointestinal disorders is also considered to be plausible based on the anti-inflammatory, gastro protective activities observed *in vitro* test (Tadić *et al.*, 2012). Data

indicate that *Sideritis* species act as a spasmolytic on intestinal smooth muscle, supporting their uses in gastrointestinal disorders (Brankovic *et al.*, 2011)

The available toxicological data and the results of the Ames tests performed according to the bracketing/matrixing-model support the positive safety profile of *Sideritis scardica*.

## **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**

Flavonoids and phenolic acid metabolites excreted in human urine after ingestion of *Sideritis scardica* decoction with characterized polyphenolic composition were studied. The study with ten volunteers was performed in two phases. First, the volunteers followed a polyphenol-restricted diet and received the *Sideritis scardica* decoction with following daily urine collection. In the second phase, the *Sideritis* decoction was used in combination with a normal diet with following daily urine collection (also 24 hours after ingestion). In the *Sideritis* decoction 31 different metabolites of hypolaetin, methylhypolaetin, isoscutellarein, methyliso-scutellarein, and apigenin and 32 phenolic acid metabolites were identified and the total content was found to be  $1450 \pm 8$  mg in 8 g of dried aerial part of *Sideritis scardica* used for the preparation of the decoction. The authors reported about the urinary excretion of polyphenol metabolites which corresponded to 5% (n/n) of the intake of polyphenols by the decoction. Flavonoid metabolites were dominant in urine samples with 87-94% of the total polyphenolic metabolites content. The most abundant metabolites were methylhypolatein and methylisoscutellarein. The urinary excretion of isoscutellarein was 10 times higher than that of hypolaetin and apigenin showed high urinary excretion (Petreska & Stefova, 2013).

### **4.2. Clinical efficacy**

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

No data available.

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

No data available.

There is a lack of clinical research, assessing the effects of mountain tea herb and rigorous randomised controlled clinical trials are required.

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

None reported

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

No data available

There is a lack of controlled clinical studies with preparations containing *Sideritis* sp. (*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L.)

The uses are made plausible by the long-standing use, having regard also to existing *in vitro* pharmacological data.

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

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

No data available.

#### **5.2. Patient exposure**

No data available.

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

No data available.

#### **5.4. Laboratory findings**

No data available.

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

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

No data on the oral use in children and adolescents are available, therefore mountain tea can be intended only for adults and elderly.

##### **5.5.2. Contraindications**

Hypersensitivity to the active substance or to other plants of the Lamiaceae (Labiatae) family.

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

The use in children and adolescents under 18 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**

None reported

### 5.5.5. Fertility, pregnancy and lactation

No fertility data available.

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

### 5.5.6. Overdose

No cases of overdose have been recovered in the scientific literature.

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

No data in the literature search.

### 5.5.8. Safety in other special situations

No data in the literature search.

## 5.6. Overall conclusions on clinical safety

In the absence of adequate data on the use in children and adolescents, the oral use of mountain tea herb is intended only for adults and elderly.

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

No fertility data available.

Moreover no adverse effects have been reported, showing enough safety data for the proposed traditional use of herbal medicinal products containing mountain tea, in the conditions for a safe use found in the monograph.

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

Based on the data documented in the assessment report, a European Union herbal monograph is established on the traditional uses of the comminuted herbal substance of *Sideritis scardica*, *Sideritis clandestina*, *Sideritis raeseri* and *Sideritis syriaca*, herba. The traditional uses of this preparation of these *Sideritis* species fulfils the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2001/83/EC as amended. None of the data fulfill the requirements to demonstrate a well-established medicinal use with recognised efficacy for preparations containing *Sideritis* sp., thus the monograph is restricted to traditional uses.

*Sideritis scardica*, *Sideritis raeseri*, *Sideritis syriaca* and *Sideritis clandestina* have been described as very closely related botanically endemic species of the Balkan Peninsula and have been traditionally used as healing aromatic herbal teas in folk medicine of the Balkan countries. 'Mountain teas' ('Pirin tea' or 'Mursalski tea') often used for domestic use and consumption have been described mainly for the relief of cough of different origin but mainly associated with cold. Furthermore, it is reported that *Sideritis scardica*, *Sideritis raeseri*, *Sideritis syriaca* and *Sideritis clandestina* are traditionally used for the treatment of inflammation, gastrointestinal disorders, and cough associated cold. Pharmacological

properties of the plants found in relevant scientific literature like the anti-inflammatory, gastro protective, spasmolytic effects and anti-microbial activities could support these indications.

The uses are made plausible by the long-standing use and experience, having regard also to existing *in vitro* pharmacological data.

There is a lack of controlled clinical studies with preparations containing *Sideritis* sp. (*Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L.).

The following indications are proposed for the European Union monograph on *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L., herba:

1. Traditional herbal medicinal product used for the relief of cough associated with cold.
2. Traditional herbal medicinal product used for the relief of mild gastrointestinal disorders.

On the basis of the long-standing use the use of the comminuted herbal substance of *Sideritis scardica*, *Sideritis clandestine*, *Sideritis raeseri* and *Sideritis syriaca* are regarded not to be harmful in the uncomplicated specified disorders mentioned above.

In the absence of adequate data in adolescents and children, the oral use of preparations containing *Sideritis scardica* Griseb.; *Sideritis clandestina* (Bory & Chaub.) Hayek; *Sideritis raeseri* Boiss. & Heldr.; *Sideritis syriaca* L. herba are intended only for adults and elderly.

In the absence of available data, it is recommended not to use mountain tea containing traditional herbal medicinal products during pregnancy and lactation.

The data on safety are considered sufficient to support a European Union list entry for the above mentioned herbal preparation of *Sideritis scardica* Griseb, herba and indications.

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

## **Annex**

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