

5 April 2016 EMA/HMPC/41109/2015 Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Helichrysum arenarium* (L.) Moench, flos

Final

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)	Helichrysum arenarium (L.) Moench
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	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

According to Flora Europaea (Clapham *et al.*, 1976, monograph on Helichrysum Miller) *Helichrysum arenarium* (L.) Moench is a herbaceus perennial 8-30 (-50) cm. Plant not sweet-smelling. Stems erect or ascending from the stout, branched stock, appressed-lanatae, greish-white. Leaves more or less densely whitish-tomentosae; lower 50-70 mm, obovatae-oblong, obtuse, 1 - veined, narrowed into the petiole; upper narrowly oblong-; lanceolatae to filiform, subacute, not apiculatae. Non flowering shoots with rosettes of broadly spathulatae, petiolate leaves. Inflorescence 2-5 cm across; involucre 4-5 mm in diameter, subglobose, becoming hemispherical, yellow to reddish-orange, shining; bracts closely imbricate, the inner 5 times as long as the outer, narrowly spathulatae, the outer suborbicular, somewhat tomentosae at base. Outer florets hermaphrodite. Achenes scabrid. 2n = ?14, 28. Grows on dry sandy places, from Netherlands, south Sweden and Estonia southwards to south Germany, south Bulgaria and west Kazakhstan.

There were two *Helichrysum arenarium* (L.) Moench subspecies described:

- *subsp. arenarium*: upper leaves oblong-lanceolatae to broadly linear; margin usually flat; throughout of the species;
- subsp. ponticum (Velen.) Clapham, Bot. Jour. Linn. Soc. 70: 18 (1975) (*H. arenarium* var. ponticum Velen), with upper leaves narrowly linear, margins strongly revolute; from west shore of Black Sea (Clapham *et al.* 1976).

IPNI database registered following subspecies of *Helichrysum arenarium* (L.) Moench:

- subsp. aucheri Boiss P.H. Davis & Kupicha Notes Roy. Bot. Gard. Edinburgh 33 (2); 239.1974 (Index Kewensis);
- subsp. erzincanicum P.H. Davis & Kupicha Notes Roy. Bot. Gard. Edinburgh 33 (20: 240.1974 (Index Kewensis);
- subsp. ponticum (Velen.) A.R. Clapham Bot. J. Linn. Soc. 70 (1): 18. 1975 (Index Kewensis);
- subsp. rubicundum (K. Koch) P.H. Davis & Kupicha Notes Roy. Bot. Gard. Edinburgh 33 (2); 239.1974 (Index Kewensis).

Recently, on the basis of phylogenetic studies some authors suggested that Euro-Asiatic *H. arenarium* subspecies could be separated into two groups. One is the Euro-Asiatic ssp. *arenarium*; the stable chromosome count taxon observed in Poland, Slovak Republic, Czech Republic, Bulgaria and Sweden (Galbany-Casals *et al.*, 2009). Most of the Helichrysi flos from EU countries belongs to this subspecies. The other group could be *ssp. aucheri*, observed e.g. in Turkey.

Helichrysi flos, according to the national monograph in Farmakopea Polska IX (2011) and Farmakopea Polska X (2014), contains the whole, dried inflorescence of sandy

everlasting *Helichrysum arenarium* (L.) Moench. Inflorescence is composed of flowerheads collected in umbel-shaped panicles, with parts of stalks up to 1 cm. Flowerheads diameter of 4-8 mm, stems densely hairy, greenish-grey. Leaves of head cover (the bracts of involucre) are numerous, imbricately arranged in 6-7 rows, dry, membranous, lemon yellow, rarely orange or whitish. External leaves elliptic-ovatae, with a length of about 3 mm, inner -

spatulate, blunt, sometimes jagged on top. The bottom of the flowerhead flat, hairless, with a dimpled surface. Nearly all of the flowers are tubular with the length of 3 mm, hermaphrodite. In the outer

whorl sometimes female. Flower crown yellow orange, campanulate expanded on top, completed with a 5 teeth. Stamens 5, ovary cylindrical or egg-shaped in a bottom. At the top of the ovary there is one whorl of lemon yellow flare pappus. Features: odor weak, characteristic.

In Pharmacopoea Helvetica (2012), in the monograph of Immortelle jaune (fleur's de) there is the following description of the herbal substance: "The corymbs formed by yellow flower heads forms tomentose peduncles, they are compact. The bracts of the involucre, lightly wraps many florets of yellow orange colueur. The flower heads are arranged in corymbose racems isolated or grouped on small tomentose stems. They usually measure 4 to 6 mm, and are fully yellow colored. The bracts of the involucre are numerous, imbricate 6 to 9 circles, the outside are oval, more and more narrow and finally lanceolate inwards. All of them contain of more thicker scarious median part (mesophyll). The receptacle is hairless and generally does not include ray florets. The tubular flowers are numerous, usually 6 mm to 7 mm long. The tube is narrow and elongated, divided in the front into 5 triangular teeth. The pappus is hairy, almost as long as the corolla tube."

Dried flower heads of Flos Helichrysi arenarii are also described in WHO monographs on medicinal plants commonly used in the Newly Independent States (WHO, 2010).

Phytochemical investigation of sandy everlasting flower was undertaken by Jerzmanowska (Jerzmanowska, 1956; Jerzmanowska & Grzybowska, 1958), continued by Grzybowska and followed by Hänsel and Heise and Vrkoč, Herout and Šorm (Szadowska, 1962). Hänsel and Heise isolated two glycosides from sandy everlasting named helichrysin A and helichrysin B (Szadowska, 1962). Helichrysin A more currently was separated into two isomeric forms (2S)-helichrysin A and (2R)-helichrysin A (Wang *et al.*, 2009a), helichrysin B was found to be (-)-naringenin-5- β -D-glucoside = salipurposide. Hänsel *et al.* has found the glycoside isosalipurposide (Szadowska, 1962).

Generally in the inflorescence there are three types of flavonoids: flavanones, flavones and flavonols (Czinner *et al.* 1999 and 2002; WHO, 2010). The flavanone derivatives are naringenin, naringenin-5-*O*-glucoside [(+)-naringenin-5- β -D-glucoside = helichrysin A, (-)-naringenin-5- β -D-glucoside = helichrysin B = salipurposide, naringenin-4'-*O*-glucoside and naringenin-5-*O*-diglucoside. The flavones and flavonol compounds of Helichrysi flos are as follows: apigenin-7-*O*-glucoside, apigenin, luteolin, luteolin-7-*O*-glucoside, kaempferol, kaempferol-3-*O*-glucoside, kaempferol-3-*O*-diglucoside, quercetin-3-*O*-glucoside, 3,5-dihydroxy-6,7,8-trimethoxyflavone (Czinner *et al.*, 2002). A characteristic, dominating compound of the inflorescence is isosalipurposide (2',4,4',6'-tetrahydrochalcon-6'-*O*-glucoside) (Czinner *et al.*, 2002).

The major phenolic acids of the inflorescence are caffeic, chlorogenic and ferulic acids (Dombrowicz *et al.* 1994, Bryksa-Godzisz *et al.*, 2006). Coumarins identified in Helichrysi flos are scopoletin, umbelliferon and aesculetin (Derkach *et al.*, 1986).

Bryksa-Godzisz *et al.* (2006) determined the phenolic acid and the flavonoid content in Helichrysi flos collected from 22 places in east Poland, along the Bug river. The medium content of chlorogenic acid was 0.314 g/100 g and ferulic acid 0.232 g/100 g. The medium flavonoid contents in the samples were: isosalipurposide 9.095 g/100 g (dominating component); apigenin-7-glucoside 0.215 g/100 g; naringenin 0.098 g/100 g; apigenin 0.090 g/100 g; isoquercitrin 0.076 g/100 g; luteolin 0.024 g/100 g; quercitrin 0.021 g/100 g; kaempferol 0.010 g/100 g. Helichrysi flos also contains yellow coloured compounds with an α-pyrone structure (Pyran-2-one), named arenol, 3-[2,3,6-trihydroxy-4-acetyl-5-(3,3-dimethylallyl)benzyl]-4 hydroxy-5,6-dimethyl-2H-pyran-2-one and homologous homoarenol 3-[2,3,6-trihydroxy-4-acetyl-5-(3,3-dimethylallyl)benzyl]-4 hydroxy-5-methyl-6-ethyl-2H-pyran-2-one (Vrkoč *et al.*, 1971).

Recently, researchers from China and Japan have conducted re-examination of flavonoids from commercial samples of Helichrysi flos from Poland and have separated a number of new compounds from a methanolic extract. Their structures were elucidated by NMR-CD methods. Wang *et al.* (2009a) isolated 6 new flavonone compounds, among them 2R,3R-dihydrokaempferol 7-*O*- β -D-glucoside, (2S)-naringenin-7-*O*- β -D-glucopyranoside and helicioside A. The same research group (Wang *et al.*, 2009b) isolated some new flavone compounds, among them new glucopyranosides: luteolin 3'-*O*- β -D-glucopyranoside, luteolin 6-hydroxy-7-*O*- β -D-glucopyranoside and kaempferol 3-*O*-(3- β -D-glucopyranosyl)- β -D-glucopyranoside. Morikawa *et al.* (2009) isolated a group of new glycosides named everlastosides A to E.

The essential oil obtained from Helichrysi flos in Europe is usually small in amount, 0.05% (Blashek *et al.*, 2013) however a sample from Caucasus region contained 0.09% (Czinner *et al.*, 2000). The analysis of the composition of the essential oil from Central Europe has been conducted by several authors (Czinner *et al.*, 2000; Judzentiene & Butkiene, 2006; Radušienė & Judžentienė, 2008) and indicates that difference exists in the oil obtained from different geographic locations. Samples from Caucasus region analysed by Czinner E *et al.* (2000) showed presence of 1.5% of β -asarone, which was not known in the samples from Central Europe. The most recent analysed samples, collected around Kharkov in Ukraine (Baranchikova *et al.*, 2014) indicated asarone content. There were also differences between volatile fractions from different parts of the plant. In the flowers they found 35.5 mg/kg of asarones but in stems with leaves 135.5 mg/kg β -asarone. The results are preliminary and authors concluded that further investigation was needed for the work, but they suggested that the whole overground plant might contain considerably more asarones than inflorescences only.¹

Traditionally sandy everlasting flower has been used in Europe in the form of water extracts, infusions and decoctions. Lemberkovics *et al.* (2002) analysed the content of herbal teas prepared from commercial samples of Helichrysi flos, from Hungary, Poland and Germany. The infusions were prepared from 5 g plant material in 200 ml of boiling water, infused under covered vessel during 30 min. After this time, the total flavonoid contents were determined (spectrometric method, DAB10) between 47 mg/l and 67 mg/l and total polyphenols content between 1,200 mg/l and 1,730 mg/l. The mean values (%) of polyphenol and flavonoid dissolution were 80.32% and 21.65%, respectively (temperatures of infusions after 30 min were not monitored).

Herbal preparation

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.

Not applicable

1.2. Search and assessment methodology

The literature search was performed in Pubmed, Micromedex and TOXLINE. Because of the large dispersion of useful information, different key words were used: *Helichrysum arenarium*, *Helichrysum arenarium*, *Helichrysum arenarium* subsp. aucheri, *Helichrysum arenarium* subsp. ponticum, *Helichrysum arenarium* + phytochemical, *Helichrysum arenarium* essential oil, *Helichrysum arenarium* + phytochemical, *Helichrysum arenarium* essential oil, *Helichrysum arenarium* subsp.

¹ Taking into account that the samples from Eastern Europe, Turkey and Caucasus regions may contain more volatile oil or the oil with asarones it should be adviced to prepare decoction, boiled at least 10 min in open vessel, not to infuse under cover.

+ toxic, sandy everlasting, Immortelle, Flos Stoechados citrini, Stoechados flos, Gnaphalium arenarium.

The search was also performed in manuals in the area of phytotherapy starting from 1933 (Polish libraries - "Phytotheraphy" term was used) and in books, book chapters and articles in Journals, letters, posters, proceedings, acts of law which are in the area of Google and Google Scholar activities.

Search engines used: Google and Google Scholar. Extensive use of general search engines gave most of the data.

Scientific databases: ScienceDirect (www.sciencedirect.com), International Plant Names Index, The Plant List (<u>www.theplantlist</u>), Germplasm Resources Information Netwek (GRIN) United States Department of Agriculture, part. GRIN Taxonomy of Plants (<u>www.ars-grin.gov</u>).

Medical databases: PubMed, Micromedex.

Toxicological databases: TOXLINE (TOXNET database).

Pharmacovigilance resources: Not available for herbal tea products. One PSUR for a combination product was available.

Data from EU and non-EU regulatory authorities: Not available.

Other resources: PhD and diploma thesis.

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

Active	Indication	Pharmaceutical form	Regulatory Status
substance			
Sandy	Traditional herbal medicinal	Herbal tea	Traditional use
everlasting	product used in digestive	Decoction of one spoonful (1.5	registration since
flower,	complaints as a choleretic.	g) in 200-250 ml of water.	2010.01, Poland
comminuted	The indication is based	Drink warm decoction 2-3	
	exclusively on long term use.	times daily	
Sandy	Traditional herbal medicinal	Infusion of 3 g of the	Traditional use
everlasting	product used in mild dyspeptic	comminuted herbal substance	registration since
flower,	disorders.	in sachet (10-15 min) to be	2010.03.19,
comminuted		drank three times daily,	Lithuania
		15-30 min before meals.	
		Not to be used for more than	
		2 weeks	

 Table 1: Overview of data obtained from marketed medicinal products

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

Poland

Helichrysi flos is contained in a product in a form of oral liquid, registered in Poland, containing in 100 g: Extractum compositum (1:2) ex: Helichrysi inflorescentia, Matricariae flore, Coriandri fructu, Sambuci fructus (24:15,5:7,5:3) extraction solvent ethanol 60% (V/V) 89 g and Taraxaci intractum (1:1) extraction solvent ethanol 60% (V/V) 11 g.

Indication: The product is traditionally used in symptoms of indigestion as choleretic. Posology: Adults 1 teaspoonful 3 times daily. Adolescents 14-18 years, 3 times daily ½ teaspoonful Product have been on the market since before 1976.

Austria

Helichrysi flos is used in a form of tea mixtures prepared in pharmacies.

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

There are two products present on the Polish market in a category of "Pharmacopoeial products."

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

Outside the EU countries Helichrysi flos preparations have been used first in Soviet Union and in countries of the former USSR.

Szadowska (1962) discussed the pharmacological investigation of an extract of *Helichrysum arenarium*, conducted by Petrovski *et al.*, but there was no detailed information on this preparation from those times. The product was firstly present on the market in Russia and in Ukraine. The same publication was later cited by Turova & Sapozhnikova (1984). According to Turova & Sapozhnikova (1984) the extract contained flavonoids from sandy everlasting flower in a form of amorphous yellow powder or tablets (0.05 g). It has been used in chronic liver inflammation, diseases of the gallbladder and biliary ways, like cholecystitis, cholangitis, hepatocholecystitis. Usually it was applied in single oral doses 0.05 g 3 times a day, 30 min before meals. If necessary the dose could have been increased to 0.1 g (two tablets) 2-3 times daily. The doses in children over 7 years of age were the same. The therapy lasted 10-40 days. Currently according to the database of VIDAL-EKSPERT (www.webvidal.ru), the Tipowaja kliniko-farmakologitcheskaja statja (typical summary of product characteristics) contains the following medical data: *Pharmacological activities: Herbal preparation exhibiting bile secretion stimulatory, choleretic, cholekinetic, antiinflammatory, antibacterial, spasmolytic and wound healing activities.*

Increases the secretion of the bile and the content of bilirubin, increases the tone of the gallbladder and promotes the bile flow. It has a relaxing effect on the smooth muscle sphincters of the gallbladder and biliary tract, and changes the viscosity and the chemical composition of bile.

It stimulates the secretion of the gastric juice and slows the stomach and intestine emptying, improves the digestion. It activates the exocrine activity of the pancreas; dilates the blood vessels of the intestine. It promotes the release of cholesterol in the bile, has hypocholesterolemic effect; possesses antibacterial activity against Gram-positive bacteria.

Indications: hepatocholecystitis, cholecystitis, biliary dyskinesia.

Dosage: 30 min before a meal (with a small amount of warm water), 1 tablet 3 times a day, if necessary - 2 tablets 2-3 times a day. The treatment course - 10-40 days.

Side effects: allergic reactions, increased blood pressure in patients with hypertension.

Contraindications: hypersensitivity, cholelithiasis, obstructive jaundice.

Drug Interactions: increases the activity of metronidazole and aminoquinolyl in the treatment of giardiasis.

Turova & Sapozhnikova (1984) have described also

- the use of the dry extract, *Extractum florum Helichrysi sicccum* in a form of granulated powder; it was used in a dose of 1 g, 3 times daily, during 2-3 weeks.
- the decoction of sandy everlasting flower *Decoctum Helichrysi* made of 10 g comminuted flowers in 200 ml of water, heated on boiled water bath during 30 min. The decoction was used in a dose of one spoonful (10 ml) 3-4 times daily 15-20 min before meals.
- a fluid extract, *Extractum Helichrysi arenarii fluidum*, 3 times daily 1 teaspoonful (5 ml) and herbal teas in a form of infusions; contained: Flor. Helichrysi arenarii 30.0 part and Herbae Absinthii, Fructus Foeniculi, Folium Menthae piperitae a.a. 20.0 parts.

The decoction and the dry extract were used in Russia as a cholagogue in the following indications: cholelithiasis, chronic cholecystitis and hepatitis and biliary dyskinesia. A warm decoction was also used: 10 g per 250 ml of water, 1/2 of glass (100-125 ml) 2-3 times per day (Turova & Sapozhnikova , 1984).

The dry extract of Helichrysum (*Extractum florum Helichrysi arenarii siccum*) was in a form of granulated powder, containing an extract of the flowers of Helichrysum, mixed with lactose (1 part drug corresponds to 4 parts of a Helichrysum flower (DER 4:1)). Single dose 1 g, three times a day. The average duration of treatment was 2-3 weeks (Turova & Sapozhnikova, 1984).

Granules of Helichrysum flowers were also used: 2 g granules (9-10 pieces) pour with a glass of hot water, bring to a boil under cover on a low heat, leave in a warm place for 30 minutes, cool and filter. Take 1/2 of glass (100-125 ml) 2 times a day, 30 min before meals (Tswetki bessmertnika pescanego - <u>www.prodenas.ru</u>).

Species cholagogae (herbal mixture). Ingredients: immortelle flowers (Helichrysi flos) 4 parts, shamrock leaf (Trifolii albi folium) 3 parts, peppermint leaves (Menthae piperitae folium) 2 parts, coriander fruits (Coriandri fructus) 2 parts. One tablespoonful brewed with 2 cups of boiled water, 20 min, strain. Take 1/2 cup 3 times a day for 30 min before meals (Turova & Sapozhnikova, 1984).

Species cholagogae N 2 (herbal mixture). Ingredients: immortelle flowers (Helichrysi flos) 4 parts, yarrow grass or leaves (Millefolii herba/folium) 2 parts, peppermint leaves (Menthae piperitae folium) 2 parts, coriander fruits (Coriandri fructus) 2 parts. Dosing is the same as the Species cholagogae (Enciklopedja lekarstv i tovarov aptetschnogo assortimenta - <u>www.rlsnet.ru</u>).

There is a WHO Monograph Flos Helichrysii arenarii in *WHO monographs on the medicinal plants commonly used in the Newly Independent States* (WHO, 2010), where the main suppliers of the herbal substance were mentioned: countries of the former USSR, Poland and Turkey.

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

In two EU countries where sandy everlasting flower products are present on the market as monocomponent herbal medicinal products, there are documented data on the medicinal use of this herbal substance. Kažemekaitis (2010) has compiled the historical data on the use of medicinal plant species in Lithuania since 1873. Helichrysum arenarium was mentioned in the regulations on

pharmaceutical taxa (it's been used in pharmacies) in 1904, 1911, 1914 and, during USSR times, the monographs on Helichrysum arenarium were present in the following editions of Gosudarstvennaya Farmakopeya SSSR: ed. VII 1937, ed. VIII 1952, ed. IX 1961, ed. X 1968, ed. XI 1990. Helichrysum arenarium inflorescence was introduced to the official medicine in Poland, during the thirties of the XX century. Under a name of Flos Stoechados it was listed in the regulation on determination of prices in pharmacies on the 24th June 1938 (Rozporządzenie, 1938).

The national monograph, Species Cholagogae, contains the herbal substance, placed in Regulation of Minister of Health from 5th of January 1949 about prices in Pharmacies, in the following composition: Flos Stoechados (= Helichrysi flos) 15 parts, Herba Hyperici 15 p., Herba Millefolii 15 p., Herba Millefolii 15 p., Herba Polygoni avicularis 15 p., Radix cum herba Taraxaci 15 p., Anthodium Chamomillae 10 p., Herba Chelidonii 10 p., Folium Menthae pip. 5 p (Rozporządzenie, 1949).

Muszyński (1954) mentioned the herbal substance in his manual, under an old name Flos Stoechados which was known to contain important amounts of flavon dye, traces of essential oil and tanins. Farmakopea Polska ed. III (1954) has a monograph on Inflorescentia Helichrysi and Species Cholagogae (comprising Radix Taraxaci 35 p., Folium Menthae piperitae 15p., Herba Millefolii 15 p., Inflorescentia Helichrysi 15 p., Cortex Frangulae 15 p., Herba Chelidonii 5 p). In the last edition of Polish Pharmacopoeia Species Cholagogae contains the following comminuted herbal substances: Taraxaci officinalis radix 29.0 parts; Menthae piperitae folium 30.0 p.; Flos Helichrysi 20.0 p.; Herba Millefoli 20.0 p.; Frangulae cortex 1.0 p (Farmakopea Polska, ed. X, 2014).

Roeske (1955) in his manual of phytotherapy described two preparations: decoctions (10%) of Helichrysi flos, used as cholagogum in cholelithiasis and cholecystitis icterus (single dose of 1 spoonful (10 ml) every 2 hours) and Extractum Helichrysi fluidum (taken 2-3 times daily a teaspoonful (5 ml)).

Sandy everlasting flower have been used in Germany.

According to Wichtl (2004), the German Standard License (St. Zl. 1986, Publ. March 12, 1986) contains the following data on medicinal use:

Indications for use: For supportive treatment of non-inflammatory gallbladder complaints.

Dosage and Mode of administration: Pour boiling water over about 2 teaspoonful (3-4 g) of yellow chaste weed [Helichrysi flos]. Steep for 10 min and pass through a tea strainer. Unless otherwise prescribed, drink one freshly prepared warm cup of tea infusion, several times daily.

There was a Comission E Monograph on Helichrysi flos, (BAnz no 122, published July 6, 1988, revised September 1, 1990) containing data on medicinal use:

Uses: Dyspeptic disorders

Contraindications: Occlusion of the biliary ducts. In case of gallstones to be used only after consultation with a doctor.

Side effects: None known.

Interactions with other drugs: None known.

Dosage: Unless otherwise prescribed average daily dosage is 3 g of dried flowers or equivalent preparations.

Mode of administration: Cut dried flowers for tea infusions as well as other galenical preparations for oral use

Action: mild choleretic (Wichtl, 2004; Blumenthal, 1998).

There is a monograph in the PDR for Herbal Medicine under the commonly used American name of Immortelle (Gruenwald, 2007).

There is a WHO monograph on Flos Helichrysi arenarii in the WHO monographs on medicinal plants commonly used in the Newly Independent States, (WHO, 2010).

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form	Reference
10% decoction Two preparations traditionally used in EU countries	Used as cholagogum in cholelithiasis and cholecystitis icterus	10% decoction single dose 1 spoonful (10 ml) every 2 hours.	Roeske, 1955
Flavonoida florum Helichrysi arenarii [counted as a sum of 70% of flavonoids]. Available in a form of 50 mg tablets Product never been used in EU countries	In chronic liver inflammation diseases, gallbladder and biliary ways diseases like cholecystitis, cholangitis, hepatocholecystitis	Usually in single oral doses 0.05 g 3 times a day, 30 min before meals. If necessary the dose could be increased to 0.1 g (two tablets) 2-3 times daily. The doses in children over 7 years of age were the same. Therapy lasted 10-40 days.	Turova & Sapozhnikova, 1984
Extractum florum Helichrysi sicccum Preparation never been used in EU countries	In chronic liver inflammation diseases, gallbladder and biliary ways diseases	 1 part of drug corresponds to 4 parts of a Helichrysum flower, DER 4:1. Used in a dose of 1 g 3 times daily, during 2-3 weeks 	Turova & Sapozhnikova, 1984
<i>Extractum Helichrysi</i> <i>arenarii fluidum</i> Preparation mentioned in Polish literature, but never been officially present on the market	In chronic liver inflammation diseases, gallbladder and biliary ways diseases	3 times daily 1 teaspoonful (5 ml)	Turova & Sapozhnikova, 1984
Decoctum Helichrysi	In chronic liver inflammation diseases, gallbladder and biliary ways diseases	The decoction made of 10 g comminuted flowers in 200 ml of water (5%), used in a dose of one spoonful (10 ml) 3-4 times daily 15-20 min before meals.	Turova & Sapozhnikova, 1984
Infusion	For supportive treatment of non-inflammatory gallbladder complaints.	Pour boiling water over about 2 teaspoonful (3-4 g) of yellow chaste weed [Helichrysi flos]. Steep for 10 min and pass through	German Standard License, 1986 (Wichtl, 2004)

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form	Reference
		a tea strainer. Unless otherwise prescribed, drink one freshly prepared warm cup of tea infusion, several times daily.	
Infusion	Dyspeptic disorders	Cut dried flowers for tea infusions as well as other galenical preparations for oral use; average daily dosage is 3 g of dried flowers or equivalent preparations	Comission E Monograph, 1988 (Wichtl, 2004; Blumenthal, 1998)

2.3. Overall conclusions on medicinal use

On the base of the available data on herbal medicinal products which are available in European Union countries it is reasonable to accept traditional use of a decoction and an infusion, made from Helichrysi flos.

Herbal preparation	Indication	Posology, Strength	Period of medicinal use
Pharmaceutical form			
Herbal tea,	Traditionally in	Herbal tea	Traditional use
decoction	digestive disorders	Decoction of 1.5 g in 200-	registration since
	as a choleretic	250 ml of water.	2010, Poland. On the
		Drink warm decoction 2-3	base of tradition since
		times daily	before 1976
Herbal tea, infusion	Traditional herbal	Infusion of 3 g of the	Traditional use
	medicinal product	cominuted herbal substance	registration since
	used in mild	(10-15 min) to be drank	2010.03.19,
	dyspeptic disorders.	three times daily, 15-30 min	Lithuania
		before meals.	
		Not to be used for more than	
		2 weeks	

3. Non-Clinical Data

The herbal substance was used in folk medicine for a long time. First pharmacological experiments on Helichrysi flos preparations were conducted in the USSR.

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

3.1.1. Primary pharmacodynamics

Cholagogue activity - In vivo

Different extracts and isolated compounds

Cholagogue activity of the flavonoid fraction of sandy everlasting and its protective effects against acute ehanolic liver intoxication in rats were observed first by Jelinek in 1960. Fractions without flavonoids did not have this effect. In the same year Grzybowska isolated kaempferol-3-glycoside (astragalin), naringenin-5- β -D(-)–glycoside (helichrysin A) and naringenin-5- β -D(±)–glycoside (helichrysin B) from sandy everlasting flower (Szadowska, 1962).

Szadowska (1962) studied the pharmacological effects of the intravenous administration of some flavonoids from sandy everlasting (4 mg/100 g) versus positive control (Decholin, deoxycholic acid) and negative control (isotonic NaCl). Intravenous administration of kaempferol-3-glycoside and naringenin-5-glycoside to rats caused a 180-185%, apigenin administration caused a 160% increase of bile secretion in comparison to baseline (100%) after 15 min (positive control decholine 294%, negative control NaCl - unchanged after 15 min). The reaction to the ether extract of sandy everlasting was (5 mg/100 g) 135% with a maximum after 30 min. According to the authors, this indicated the important role of the ether soluble aglycones. The administration of a 10% decoction (1 ml/100 g) gave a 156 % increase; 10% infusion about a 158% increase; ethyl acetate extract and ethanol extract (50 mg/100 g) caused 138% and 135% increase in bile secretion with maximums after 15 and 30 min. Generally, after intravenous administration the maximum activity appeared after 15-30 min and lasted 60-75 min.

During this investigation duodenal administration was also performed to rats. The positive control (Decholin solution) gave the strongest reaction, 240% increase in bile secretion after 15 min. Naringenin-5-glycoside and kaempferol-3-glycoside caused a 135% and a 130% increase after 60 min; and no reaction was observed in case of the water and NaCl solution. The ethyl acetate extract caused a 130% increase and the ethanol extract about 135% increase; 10% infusion and decoction similar increase about 112% after 15 min. Apigenin 8 mg/100 g gave a 150% reaction versus ether extract 125% reaction after 30 min. The maximum activity appeared after 30-60 min and lasted about 3 hours. The three flavonoids had pronounced choleretic activity.

Antispasmodic activity - In vivo/ex vivo

Different extracts and isolated compounds

Szadowska (1962) also conducted experiments on antispasmodic activity on the smooth muscle, isolated from rabbit and rat intestines and on gall-bladders isolated from guinea pigs and rabbits. They have shown that apigenin in dissolutions 10^{-6} neutralised spasms induced by BaCl₂ in 50% and in dissolution 10^{-5} in 100%; kaempferol-3-glycoside in dissolution 10^{-4} in 30-40%; naringenin-5-glycoside in dissolution 10^{-5} and ethyl acetate extract in dissolution 10^{-3} neutralised spasms induced by BaCl² in dissolution 10^{-6} . Ether extract in dissolution 10^{-5} and ethyl acetate extract in dissolution 10^{-3} neutralised spasms induced by BaCl² in dissolution 10^{-4} in 25% and 40-70%. An ethanol extract in dissolution 10^{-3} and 10^{-4} neutralised spasms induced by BaCl₂ in dissolution 10^{-5} in 75%. Apigenin and the ether extract that contains mainly apigenin, had the strongest antispasmodic activity on smooth muscles and isolated gall bladders *ex vivo*. Infusions and decoctions of sandy everlasting flower had weak spasmolytic activities.

All three flavonoids studied possessed spasmolytic activities, however the strongest spasmolytic was apigenin, weaker kempferol-3-glycoside and the weakest was naringenin-5-glycoside. In these studies, relaxant activity was observed, which was present already in the lowest tested concentration of

the extracts. Among the extracts the ether extract, containing mostly apigenin, had the strongest spasmolytic activity, weaker was the ethyl acetate extract, containing naringenin-5-glycoside and kaempferol-3-glycoside and the weakest was the ethanolic extract. The extract without flavonoids was inactive. The infusion and decoction, apart from the spasmolytic substances, seemed to contain spastic substances as well; this kind of activity was also detected in the flavonoid free water extract. All tested flavonoids temporarily decreased blood pressure in dogs. The extract without flavonoids caused weak contraction of the intestinal muscles, which resolved after the administration of atropine. Generally clear choleretic activity of the flavonoids was observed, however it was about three times weaker than the preparation Decholin (dechydrocholic acid administered as a positive control). Since then, further non clinical studies on *Helichrysum arenarium* inflorescence extracts haven't been performed.

The old works are referred in a WHO monograph (2010).

Influence on bile excretion vivo on rats in urethane narcosis.					
Herbal preparation or substance tested	Strength Dosage (in mg on 100 g of body weight); route of administration: intravenous (iv), intraduodenal (id)		Influence on bile excretion <i>in vivo</i> on rats. Bile excretion increase expressed in [%] in relation to medium value established for every animal before experiment.	Main non-clinical conclusions	
10% infusion of <i>Helichrysum arenarium</i> , flos	1ml/100g; iv		158% after 15 min	Mild choleretic	
10% infusion of <i>Helichrysum arenarium</i> , flos		2ml/100g; id	112% after 15 min	Very weak or no effect	
10% decoction of <i>Helichrysum arenarium</i> , flos	1ml/100g; iv		156% after 15 min	Mild choleretic	
10% decoction of <i>Helichrysum arenarium</i> , flos		2ml/100g; id	112% after 15 min	Very weak or no effect	
Ethanol extract (containing total flavonoid fraction)	50mg/100g; iv		135% after 30 min	Mild choleretic	
Ethanol extract (containing total flavonoid fraction)		100mg/100g; id	130% after 30 min	Mild choleretic	
Ethyl ether fraction (containing apigenin)	50mg/100g; iv		135% after 30 min	Mild choleretic	
Ethyl ether fraction (containing apigenin)		100mg/100g; id	128% after 30 min	Mild choleretic	
Ethyl acetate fraction (containing glycosides of naringenin and kaempferol	50mg/100g;iv		138% after 15 min	Mild choleretic	
Ethyl acetate fraction (containing glycosides of naringenin and kaempferol		100mg/100g; id	170% after 30 min	Mild choleretic	
Apigenin	4mg/100g; iv		160% after 15 min	Mild choleretic	
Apigenin		8mg/100g; id	150% , after 15 min	Mild choleretic	
Naringenin-5-glycoside	4mg/100g; iv		180-185% after 15 min	Mild choleretic	
Naringenin-5-glycoside		8mg/100g; id	135% after 30 min	Mild choleretic	

Table 4: Overview of the main non-clinical data/conclusions (Szadowska, 1962)

Kaempferol-3-glycoside	4mg/100g; iv			180-	185%	Mild choleretic
Kaempferol-3-glycoside	8mg/100g; id		; id	130% after 60 min		Mild choleretic
Dechol (deoxycholic acid) positive control	4mg/100g; iv			2949	% after 15 min	Strong choleretic
Dechol (deoxycholic acid) positive control		8mg/100g	; id	240%	% after 30 min	Strong choleretic
Spasmolytic effects ex vivo	, on gall blader	s isolated fro	om guinea pig	js or	rabbits	
Herbal preparation or substance tested	baration or Substance or BaCl ₂ tested preparation concert concentration n		BaCl ₂ Experiment ex- isolated from rabbits Spasmolytic		vo, on gall bladers nea pigs or Lowest	Main non-clinical conclusions
			effect gall bladders isolated fron guinea pigs	n [%]	spasmolytic concentration on intestines smooth muscles isolated from rabbits	
10% infusion or decoction of Helichrysum arenarium flos	10 ⁻³ 10 ⁻³	10 ⁻⁴ 10 ⁻⁵	5 75			Mild spasmolytic
neneni ysun arenanani, nes	10 ⁻³	10	75		10 ⁻³ (80%-90%)	Weak spasmolytic
Ethanol extract (containing total flavonoid	10 ⁻³ 10 ⁻⁴	10 ⁻⁴ 10 ⁻⁴	100 15			Mild spasmolytic
fraction)	10-4				4 x 10 ⁻³	Weak spasmolytic
Ethyl ether fraction	10-3	10-4	25			Mild spasmolytic
	10-6	4			10 ⁻⁵	Mild spasmolytic
Ethyl acetate fraction	10-3	10-4	40-70		<u>^</u>	Mild spasmolytic
naringenin and kaempferol	10-4				4 x 10 ⁻³	Weak spasmolytic
Apigenin	10 ⁻⁶ 10 ⁻⁵	10 ⁻⁴	50 100			Mild spasmolytic
	4 x 10 ⁻⁶				5 x 10 ⁻⁵	Mild spasmolytic
Naringenin-5-glycoside	5 x 10 ⁻³ 5 x 10 ⁻³	10 ⁻⁵ 10 ⁻⁶	10 90			Mild spasmolytic
	5 x 10⁻³				2 x 10 ⁻³	Weak spasmolytic
Kaempferol-3-glycoside	10 ⁻⁴	10 ⁻⁴	25-30			Mild spasmolytic
	4 x 10 ⁻⁴				10-4	Weak spasmolytic
Water fraction	10 ⁻³ -10 ⁻⁴	-	- (Constriction	on)		Constriction
	10 ⁻⁴				- (Constriction)	Opposite effect (constriction)

3.1.2. Secondary pharmacodynamics

Antioxidant activities and radical scavenging - In vitro

Water extracts

It was supposed that the choleretic, hepatoprotective and "detoxifying" activities of the inflorescence of *Helichrysum arenarium* (L.) Moench, flos (syn. Stoechados flos) which have been known for a long time from herbal medicine, could be related to the antioxidant properties of its main phenolics, flavonoids (Czinner *et al.*, 1999). The authors studied the antioxidant properties of the lyophilised water extracts from the inflorescences of sandy everlasting, and determinated the total polyphenol and flavonoid contents in Helichrysi flos water extracts as well as in lyophilised water extracts. The hydrogen-donating ability, reducing power property and total scavenger activity of the lyophilisate were determined using spectrophotometric and chemilumenescence methods. H-donor activity of the lyophilisate scavenger capability were lower than that of silibilin. The flavonoid content determined in the lyophilisate was 0.47% and the authors suggested that this concentration of flavonoids may be of

therapeutic effect. The antioxidant properties of the lyophilised water extracts from the dried inflorescence of *Helichrysum arenarium*, with different polyphenol and flavonoid contents were further studied on microsomal fractions of rat liver. Enzymatically induced lipid peroxidation and NADPH cytochrome C-reductase activity in liver microsomes were measured by a spectrophotometric method. The extracts had a weak free radical scavenging activity in the microsomal fractions of rat liver at a concentration of 1 µg/ml measured by a chemiluminometric method. The activity was comparable to that of the flavonoid silibinin (Czinner *et al.*, 2000). In further work the authors measured their scavenging activity in the H_2O_2/OH -luminol-microperoxidase system, by a chemiluminometric method. The results were compared with the activity of silibinin. They observed that the same lyophilisates inhibited NADPH-induced lipid peroxide formation at a concentration of 20 µg/ml and stimulated NADPH cytochrome C reductase in rat liver microsomes at a concentration of 100 µg/ml. The extracts were more effective than silibinin at the tested concentrations (Czinner E *et al.* 2001).

Methanolic extracts

Methanol extracts of *Helichrysum* species were screened *in vitro* for antioxidant activity by two complementary test systems (2,2-diphenyl-1-picrylhydrazyl radical (DPPH) free radical-scavenging and β -carotene/linoleic acid). In the first test system, the extracts showed no antioxidant activity. In the second test system, inhibition rates of the oxidation of linoleic acid were comparable to those of the synthetic antioxidant butylated hydroxytoluene (96%). The author suggested that it could be useful to consider the use of the extract as an alternative antioxidant for the food processing industries (Tepe, 2004).

Subfractions of the dried methanolic extract from inflorescences of Helichrysum arenarium, obtained with ethyl acetate (extract A), diethyl ether (extract B) or via alkaline hydrolysis and then extracted with diethyl ether (extract C). Extracts (A), (B) and (C) were evaporated under reduced pressure to obtain the dry residues A, B and C which were further investigated for phenolic compound content by thin-layer chromatography and high-performance liquid chromatography (HPLC), as well as for 2,2-diphenyl-1-picrylhydrazyl-antiradical activity. Residue C exhibited stronger antiradical properties than non-hydrolysed residues A and B. HPLC analysis showed a greater increase in the strong antioxidant, caffeic acid, in residue C, resulting in an increase in the antiradical activity observed with residue C (Sroka *et al.*, 2004).

Albayrak *et al.* (2010a, 2010b) investigated the antioxidant activity of three subspecies of *Helichrysum arenarium* (L.) Moench: *subsp. erzincanicum* Davis & Kupicha, *subsp. rubicundum* (C. Koch.) Davis & Kupicha and *subsp. aucheri* (Boiss) Davis & Kupicha, in two complementary test systems, DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging and phosphomolybdenum assay. The plant material for the study was collected in Turkey. The authors have used the whole overground plant parts, not only inflorescence, which was extracted (10 g) using a Soxhlet type extractor with 100 ml methanol (MeOH) at 60 °C for 6 h. However, the authors found antioxidative activity and some of flavonoids which are characterictic to inflorescence also, like apigenin, apigenin-7-glucoside, naringenin, luteolin. This work indicated also large differences in phenolic compounds (ex. chlorogenic acid) between *Helichrysum arenarium* subspecies.

Antimicrobial activities - In vitro

Flavonoid fraction

First investigations of the antimicrobial activity of the flavonoid fraction of sandy everlasting were conducted in the USSR, where the preparation was observed to be active against a group of Gram positive microorganisms, specially for Streptococci and Staphylococci and other bacteria in a

concentrations 20-40 μ g/ml which is due probably mainly to naringen (4', 5, 7-trihydroxyflavone). (Khristenko *et al.*, 1977).

Essential oil

Rančić *et al.* (2005) investigated the antimicrobial activities of a sample of *Helichrysum arenarium* essential oil obtained from University of Belgrade. The authors used biochromatography to determine concentrations active against test microorganisms: *Candida albicans* (clinical isolates), *Escherichia coli* ATCC 35218, *Micrococcus luteus* ATCC 9341, *Pseudomonas tolaasii* (isolated from *Agaricus bisporus*), *Salmonella enteritidis* ATCC 13076, *Salmonella typhimurium* ATCC 13311, *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228 and against fungi *Aspergillus niger* ATCC 6275, *A. flavus* ATCC 9170, *Cladosporium cladosporioides* ATCC 13276, *Penicillium funiculosum* ATCC 10509 and *Trichoderma viride* IAM 5061. As a positive control Bifonazole was used for *Candida albicans*, and streptomycin for bacterial species. The authors observed inhibition zones (4-14 mm diameter) in every tested bacteria. The MIC/MFC (µg/ml) for tested fungi were: *A. niger* 15/30, *A. flavus* 15/15, *C. cladosporioides* 15/15, *P. funiculosum* 30/60, *T. viride* 10/15.

Sani (2014) studied antimicrobial activities of essential oil distilled from whole dried aerial plant material of *Helichrysum arenarium* L. (subspecies not identified). The essential oil was steam distillated in an apparatus described in British Pharmacopoeia, dried and stored in sterilised vial in 4°C. Its activity was tested against bacteria: *Bacillus subtilis* ATCC 6633, *Escherichia coli* 0157 NTCC 12900, *Staphylococcus aureus* ATCC 6538 and yeasts *Saccharomyces cerevisiae* 5052 PTCC, *Candida albicans* ATCC 10231 and two fungi *Aspergillus flavus* PTCC and *Aspergillus parasiticus* PTCC 5018. MIC (in µg/ml) were following: *B. subtilis* 781.25, E.coli 97.65, *Staphylococcus aureus* 97.65, *Saccharomyces cerevisiae* 97.65, *C. albicans* 195.31, *Aspergillus flavus* 48.82, *A. parasiticus* 48.82. Bactericidal Concentrations/Minimal Fungicidal Concentrations were in a range of 390.625-6250 µg/ml. Essential oil distilled from the whole overground sandy everlasting plant may be different than from the inflorescences.

Methanolic extracts

Albayrak *et al.* (2010a, 2010b) studied antimicrobial properties of a methanolic extract of the whole overground plant parts of three subspecies of *Helichrysum arenarium* (L.) Moench: *subsp. erzincanicum* Davis & Kupicha, *subsp. rubicundum* (C.Koch.) Davis & Kupicha and *subsp.aucheri* (Boiss) Davis & Kupicha, collected in Turkey. Determination of the antimicrobial activity against 16 strains of bacteria and yeast was made using a method of diffusion on agar plates. Tested concentrations were 1%, 2.5%, 5%, 10%. Extracts of herbs of the three subspecies were active against: *Aeromonas hydrophila, Bacillus brevis, B. cereus, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Staphylococcus aureus* ATCC 29213. However, no activity was found against *Escherichia coli, Morganella morganii, Mycobacterium smegmatis, Proteus mirabilis, Yersinia enterocolitica* or *Saccharomyces cerevisiae*. The authors concluded, that the methanolic extract from the whole overground sandy everlasting plant may have rather different qualitative content than from the inflorescence.

Gradinaru *et al.* (2014) studied the activity of a methanolic extract of the dried inflorescence of *Helichrysum arenarium* (L.) Moench *subsp.* arenarium (Asteraceae). The plant material was supplied from a local market in Iasi, Romania in July 2011. The powdered plant material (20 g) was extracted with methanol and concentrated to obtain 3.54 g of crude extract. The antibacterial activity was screened using the agar diffusion method, similar to the method desribed by Albayrak *et al.* (2010 a,b). As a positive control discs with ciprofloxacin (5 µg/disc) were used. Negative controls were DMSO, sterility control, viability control. The interactions between the extract and ciprofloxacin were

assessed in terms of fractional inhibitory indices (FIC index). Antibacterial activities of the extract were: against *Staphylococcus aureus* MIC (minimal inhibitory concentration) 0.62-2.5 µg/ml (ciprofloxacine 0.25-4 x 10⁻³), strains of *Streptococcus pneumoniae* 2.5 mg/ml (ciprofloxacin 2 x 10⁻³); *Moraxella catarrhalis* 0.15 µg/ml (ciprofloxacin 0.03 x 10⁻³). Staphylococcus aureus ATCC 25923 was more susceptible to *Helichrysum* extract than *Streptococcus pneumoniae* ATCC 49619 (MIC=0.62 mg/ml and 1.25 mg/ml, respectively). The extract exhibited similar antibacterial effects against methicillin-resistant *S. aureus* and penicillin-resistant *S. pneumoniae* clinical isolates (MIC=2.5 mg/ml) showing a higher activity against ampicillin-resistant *Moraxella catarrhalis* isolate (MIC=0.15 mg/ml). However, the extract was importantly less active than ciprofloxacine, the authors examining FIC (fractional inhibitory concentration) indexes, observed synergistic effect of the extract and ciprofloxacin against *Streptococci* and additive effect against *Staphylococci*. There was no interaction against *Moraxella catarrhalis*.

Antiinflammatory activity - In vitro

Isolated compound

Appendino *et al.* (2007) found that homoarenol (isolated under a name arzanol from *Helichrysum italicum*) inhibits HIV-1 replication in T cells and release proinflammatory cytokines in LPS stimulated primary monocytes. On the basis of the observation, arzanol was identified as an important antiviral component.

Studies of Bauer *et al.* (2011) showed that homoarenol inhibited microsomal PGE_2 synthase (mPGES)-1 and potently inhibits the biosynthesis of proinflammatory lipid mediators like PGE *in vitro* and *in vivo*. This activity is regarded as a novel antiinflammatory mechanism, reviewed by Kothavade *et al.* (2013).

Diuretic activity - In vivo

The influence of the flavonoids and extracts from sandy everlasting on urination was studied in rats and dogs. The investigated substances, flavonoids were kaempferol-3-glycoside, naringenin-5-glycoside and apigenin (10 mg/100 g) in 5 ml of solution, extracts in water suspension, infusions and decoctions in water soluble form were administered to rats (150-210 g). Water was administered to the control group. Urine volumes were monitored every 15 min, during 4-7 hours. None of the flavonoids or the extracts influenced the urine elimination curve, in comparison with the control group. Decoction, infusion and various extracts of the dried herb of sandy everlasting (ether, ethanol, aqueous) were administered intraduodenally to dogs and via intragastric route to rats, at doses of 10 mg/kg bw and 50 mg/kg bw, respectively. There was no diuretic activity of the extracts observed (Szadowska, 1962).

Hypotensive activity - In vivo

Intravenous injection of ethanol, aqueous and ether extracts of dried whole plant to dogs and rats at doses of 50 mg/kg and 500 mg/kg bw, respectively, produced a hypotensive effect. This short term effect was observed only as a result of intravenous administration (Szadowska, 1962).

3.1.3. Safety pharmacology

No data available

3.1.4. Pharmacodynamic interactions

No data available

3.1.5. Conclusions

Authors of the WHO monograph (, 2010) refers mainly to the publication of Szadowska (1962) on the cholagogic and antispasmodic activities. The results of these studies support the use of infusions and decoctions of sandy everlasting flower as a mild cholagogue and weak spasmolytic in bile ducts. In the experimental conditions, after intravenous and intraduodenal administration the flavonoids: apigenin, kempferol-3-glycoside, naringenin-5-glycoside, exhibited one third of deoxycholic acid activity. Among substances investigated, antispasmodic activity has been shown for apigenin and an ethyl ether extract containing apigenin and other nonpolar aglycones. Recently, an important antiinflammatory activity of homoarenol/arzanol, present in extracts of sandy everlasting was confirmed, but preclinical data on herbal preparations are still not available.

The preparations traditionally used in Europe are water extracts, decoction and infusion. The observation of Lemberkovics on dissolution of phenolic compounds and flavonoids in the infusion, (30 minutes after infusing of the herbal substance) suggest that the phenolic compounds were still present in the water extract in significant quantity but flavonoids only in a small. This suggests that for better usage of the spasmolytic properties of the whole flavonoids, it could be justified to drink the herbal teas in a form of freshly prepared and still warm decoctions/infusions.

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

No data available

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

No systematic data available

3.3.1. Single dose toxicity

No data available

3.3.2. Repeat dose toxicity

No data available

3.3.3. Genotoxicity

There is no data on the mutagenicity of the flowers of *Helichrysum arenarium* (L.) Moench and its water extracts.

However Eroğlu *et al.* (2010) has found that decoctions, prepared by boiling the whole aerial parts of *Helichrysum arenarium* (L.) Moench subsp. *erzincanicum*, growing in Turkey (4% w/v, 5 min) induced significant changes in micronuclei percentages, at concentrations of 0.5 mg/ml and 1 mg/ml. Water soluble factor, responsible for the fenomenon, was not identified in the herb. This subspecies is known for a high content of phenolic acids (specially chlorogenic acid, Albayrak S. *et al.*, 2010a). It does not grow in Europe. Decoctions and methanolic extracts (10 g of the material in 100 ml) from of *Helichrysum arenarium* subsp. *rubicundum* and *aucheri* did not induce changes in the frequency of micronuclei. Both the decoction and the methanolic extract of the herb *Helichrysum arenarium* subsp. *erzincanicum* influenced the replication index. Fractions or substances responsible for the cytotoxicity of subspecies *erzincanicum* herb, were not identified. There were no observed effects of treatments

with *Helichrysum arenarium* subsp. *aucheri* decoction and methanolic extract on mitotic index and on cellular proliferation in human lymphocytes.

In the whole plant of another species *Helichrysum simillimum* DC, from South Africa, Elgorashi *et al.* (2008) observed mutagenic activity of the extracts. The authors peformed separation procedure, monitored by Ames test and isolated kaempferol as a component responsible for mutagenic effect.

3.3.4. Carcinogenicity

No data available

3.3.5. Reproductive and developmental toxicity

No data available

3.3.6. Local tolerance

Not applicable

3.3.7. Other special studies

No data available

3.3.8. Conclusions

There are no pre-clinical data on the reproductive and developmental toxicity. The results of the literature search, phytochemical characteristics of sandy everlasting flower and post-marketing experience do not identify any positive signal on reproductive toxicity. Traditionally used preparations are not recommended to be used in pregnancy and lactation.

There are no available data on genotoxicity and mutagenicity of water extracts, decoctions and infusions, made from *Helichrysum arenarium* (L.) Moench, flos.

3.4. Overall conclusions on non-clinical data

Available non-clinical data are based mainly on the published results of studies, handbooks and the WHO monograph. The data include results of tests regarding the influence of the decoctions, infusions, ethanolic extracts, ethyl acetate extracts, ether extracts and isolated flavonoids: apigenin, naringenin-5–glycoside, kaempferol-5-glycoside, obtained from *Helichrysum arenarium* (L.) Moench, flos, on bile excretion in rats (cholagogic activity). The results indicated mild bile excretion promoting activity. In the experiments it has been compared to 1/3 activity of deoxycholic acid (positive control). The second group of tests are studies on the influence of the upper mentioned extracts and substances on spasmolytic/antismasmodic activity on isolated guinea pig and rabbit gallbladders and rabbit and rat bowel sections. The results of the experiments indicated mild spasmolytic activity of flavonoids (specially apigenin), obtained from sandy everlasting flower and extracts (specially ether extract) and rather weak activity of infusions/decoctions.

However there are no pre-clinical data on reproductive and developmental toxicity, the bibliographic data and the phytochemical characteristics of sandy everlasting flower do not identify any positive signal on possible reproductive toxicity. Traditionally used preparations are not recommended to be used in pregnancy and lactation.

There are no available data on genotoxicity and mutagenicity of water extracts, decoctions and infusions, made of *Helichrysum arenarium* (L.) Moench, flos.

Specific data on pharmacokinetics and interactions are not available.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available

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

No data available

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available

4.2.2. Clinical studies (case studies and clinical trials)

No data available

In old Russian literature there were publications about clinical observations on gallbladder treatment with orally applied sandy everlasting herb and extract and about experiences in the use of sandy everlasting preparations in the treatment of chronic cholecystitis and liver and gall ways inflammatory diseases (Turova, 1984).

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

No data available

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no clinical studies on Helichrysi flos in the scientific literature. Therefore, Article 10a of Directive 2001/83/EC as amended (well-established use) is not considered fulfilled. There are human clinical observations of sandy everlasting preparations from very old publications. The observations were conducted on patients with inflammatory diseases of biliary system, cholecystitis, cholangitis, hepato-biliary diseases and dyskinesis. The use of the products in these indications in Eastern European countries is documented until today, however, the safe use requires medical diagnosis. The use in these inflammatory diseases without medical diagnosis would not provide adequate safety to patients and could not be regarded as plausible.

The use in digestive and mild biliary disorders is substantiated with a long tradition of use however the use in more severe ailments may need medical consultation.

5. Clinical Safety/Pharmacovigilance

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

Safety data from clinical trials are not available. There were no adverse events reported for Helichrysi flos in Poland.

5.2. Patient exposure

Current exposure

According to data on marketed authorised or registered products, herbal teas and composed preparation, in Poland and Lithuania (2010-2014), it could be estimated that in years 2013-2014 there were about 170,000 package units of products per year in turnover, containing *Helichrysum arenarium* (L.) Moench, flos, what correspond to about 1,490,000 of daily doses of the products. The combination product containing ethanolic extract of sandy everlasting flower is commonly used in Poland (2.1.1). According to its last PSUR, adverse reactions were not recorded between 2008 and 2011. The product was used in 2013 at the level of 1 299 000 daily doses. This year, herbal teas were used on the market in Poland at the level of 692,000 daily doses and in Lithuania 30,000 daily doses. Adverse reactions for Helichrysi flos preparations have not been recorded.

For data on historical exposure, see paragraph 2.2.

5.3. Adverse events, serious adverse events and deaths

Since the products were registered/authorised in Poland and Lithuania, no adverse reactions have been reported.

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

No data available

5.5.2. Contraindications

Hypersensitivity for the herbal substance. Asteraceae (Compositae) family.

5.5.3. Special Warnings and precautions for use

Due to lack of data the use in children and adolescents under 18 years of age is not recommended. In the case of bile duct obstruction the use of the product should be consulted to a doctor.

5.5.4. Drug interactions and other forms of interaction

Not known

5.5.5. Fertility, pregnancy and lactation

No fertility data available

Due to lack of adequate data the use is not recommended during pregnancy and lactation.

5.5.6. Overdose

Overdose has not been reported

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

Not known

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

There are no data on clinical safety

No adverse reactions are known in conjunction with the use of sandy everlasting flowers preparations at known and used posologies. The sensitisation after the use of herbal preparations was never observed so the allergenic potential may be small, however it is possible like for other plants in the Asteraceae family. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use in pregnancy and lactation should be not recommended.

6. Overall conclusions (benefit-risk assessment)

The use of Helichrysi flos preparations in the European countries has a long tradition and is well documented. The preparations have been in medicinal use in similar indications for many decades and have been sold in pharmacies in Europe for more than a century. They were introduced to the official medicine in the thirties in Russia, where the first clinical observations were conducted and where one of the preparations has been used for many decades. Among the countries of the European Union Inflorescentia Helichrysi was introduced to Polish Pharmacopoeia in 1954. A medical tradition in the European Union countries includes long term use of decoctions and infusions. Moreover combined herbal teas and ethanolic extracts have been used traditionally in European Union countries. Along the traditional time period the preparations have been used in similar indications: in non inflammatory biliary tract diseases and digestive or dyspeptic complaints. The traditon of medicinal use was supported also by pharmacological studies indicating mild cholagogue and weak spasmolytic activities of decoctions, infusions, extracts and flavonoids isolated from the herbal substance.

Helichrysi flos fulfil the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use according to Directive 2004/24/EC in the indications: traditionally used in digestive complaints as choleretic and also in mild dyspetic disorders.

However, the HMPC/MLWP is of the opinion indications associated with diseases of the biliary system are not appropriate for self-care and thus inappropriate for traditional herbal medicinal products.

Hence, the efficacy is plausible on the basis of long-standing use and experience of herbal teas of sandy everlasting flower for the following indication: for relief of symptoms of digestive disorders with sensation of fulness and bloating.

There are no clinical studies on Helichrysi flos in the scientific literature. Therefore, Article 10a of Directive 2001/83/EC as amended (well-established use) is not considered fulfilled.Due to lack of genotoxicity safety data, the entry on the list of herbal substances, preparations and combinations, mentioned in art. 16f of Directive 2001/83/UE is not proposed.

Although for the herbal substance preparations no signal on allergic reactions was recorded, that would indicate small potential for sensitisation, in view of the possibility of cross-sensitivity reactions, the products of *Helichrysum arenarium* flowers should be contraindicated in individuals with a known hypersensitivity to the herbal substances of other plants of the Asteraceae (Compositae) family.

Considering the long-standing traditional use of sandy everlasting flower in Europe the benefit/risk balance of the medicinal use is positive.

Annex

List of references