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Committee on Herbal Medicinal Products (HMPC)

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

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Helichrysum arenarium* (L.) Moench
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Herbal tea
Rapporteur(s)	Wojciech Dymowski
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monographon *Helichrysum arenarium* (L.) Moench, flos. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

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

- Herbal substance

According to Flora Europaea (Clapham AR 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 a dry sandy places, from Netherlands, S. Sweden and Estonia southwards to S. Germany, S. Bulgaria and W. Kazakhstan. Au, Be, Bu, Cz, Da, Ga, Ge, Ho, Hu, Ju, Po, RM, Rs, (B, C, W, K, E) Su. There were two 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 W. shore of Black Sea.

IPNI database registered following subspecies of *H. 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).

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

Helichrysi flos, according to 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 floweheads 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.

In Pharmacopoea Helvetica (ed. 2012), in a monograph 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 6mm, 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 a 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 (NIS). (WHO 2010).

Phytochemical investigation of Sandy everlasting flower was undertaken by Jerzmanowska (1958), continued by Grzybowska and followed by Hänsel and Heise and Vrkoč, Herout and Šorm. Hänsel and Heise isolated of sandy everlasting two glycosides named helichrysin A and helichrysin B. Helichrysin A more currently was separated to two isomeric forms (2S)-helichrysin A and (2R) helichrysin A (Wang Li-Bo, 2009), B was found to be (-)-naringenin-5-β-D-glucoside = salipurposide]. Hänsel et al. found glycoside isosalipurposide. Generally in the inflorescence does occur three types of flavonoids: flavanones, flavones and flavonols. (Czinner et al. 1999, 2002, WHO Monograph). The flavanone derivatives are naringenin, naringenin-5-O-glucoside [(+)-0-naringenin-5-β-D-glucoside = helichrysin A, (-)-0-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 E at et al., 2002). A characteristic, dominating compound of the inflorescence is isosalipurposide (2', 4, 4', 6'-tetrahydrochalcon-6'-O-glucoside). The major phenolic acids of the inflorescence are caffeic, chlorogenic and ferulic acids (Dombrowicz et al. 1994, Bryksa-Godzisz M et al., 2006). Coumarins identified in Helichrysi flos are scopoletin, umbelliferon and aesculetin (Czinner 2002 et al after Derkach et al. 1986). Bryksa-Godzisz M et al., (2006) determined phenolic acid and flavonoid content in Helichrysi flos collected from 22 places in east Poland, along Bug river. The medium content of chlorogenic acid was 0.314 g/100g and ferulic acid 0.232 g/100 g. The medium flavonoid contents in the samples were: isosalipurposide 9.095g/100g (dominating component); apigenin-7-glucoside 0.215g/100g; naringenin 0.098g/100g; apigenin 0.090g/100g; isoquercitrin 0.076g/100g; luteolin 0.024g/100g; quercitrin 0.021g/100g; kaempferol 0.010g/100g. Helichrysi flos contain also yellow coloured compounds with the structure of α-pyrone (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 at al., 1971).

In the last years researchers from China and Japan conducted re-examination of flavonoids from commercial samples of Helichrysi flos from Poland and separated from methanolic extract a number of new compounds. Their structures were elucidated by NMR-CD methods. Wang Li-Bo 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 Li-Bo 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, kaempferol 3-O-(3-β-D-glucopyranosyl)- β-D-glucopyranoside and Morikawa T. et al. (2009) a group of new glycosides named everlastosides A to E.

Essential oil is usually contained in Helichrysi flos in Europe in small amount, 0.05% (HagerRom, 2013) however sample from Caucasus region contained 0.09% (Czinner E et al, 2000). The analysis of the composition of the essential oil from Central Europe has been conducted by several authors (Czinner E et al, 2000, Judzentiene A. and Butkiene R, 2006, Radušienė J and Judžentienė A, 2008,) and indicates that difference exists in the oil obtained from different geographic locations. Samples from Caucasus region analyzed by Czinner E at al. 2000) showed presence of 1.5% of β-asarone, which was not known in samples from Central Europe. Last time analysed samples, collected around Kharkov in Ukraine (Baranchikova et al. 2014, abstr.) indicated content of asarones. There were also differences between volatile fractions from different parts of plant. In 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 conclude that further investigation is needed for the work, but they suggest that the whole overground plant may contain importantly more asarones that only inflorescences.

Traditionally sandy everlasting flower has been used in Europe in a form of water extracts, infusions and decoctions. Lemberkovics E et al. (2002) analysed the content of herbal teas prepared of commercial samples of Helichrysi flos, from Hungary, Poland and Germany. The infusions were prepared of 5g of in 200 ml of boiling water, infused under covered vessel during 30 min. After the time total flavonoid contents were determined (spectrometric method, DAB10) between 47mg/l and 67mg/l and total polyphenols content between 1200mg/l and 1730 mg/l. The authors found that polyphenols were dissolved in 80.32% but flavonoids in 21.65% (temperatures of infusions after 30 min were not monitored).

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

- 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 rapporteur extensively searched for available scientifical and medical databases: PubMed, Micromedex, TOXLINE. Because of large dispersion of useful information, there were used multiple simple searches with different key words: Helichrysum arenarium, Helichrysum arenarium subsp. arenarium, Helichrysum arenarium subsp. aucheri, Helichrysum arenarium subsp. ponticum, Helichrysum arenarium + phytochemical, Helichrysum arenarium essential oil, Helichrysum + toxic, Sandy everlasting, Immortelle, Flos Stoechados citrini, Stoechados flos, Gnaphalium arenarium.

Search in books contained manuals of the area of phytotherapy in Polish libraries starting from 1933 (edition of first book using a term “Phytotheraphy”) and 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 data.

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

Medical databases: The rapporteur extensively searched for available medical databases: PubMed, Micromedex.

Toxicological databases: TOXLINE (TOXNET database).

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

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

Other resources: PhD, 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

Table 1: Overview of data obtained from marketed medicinal products

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

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 teaspoon 3 times daily. Adolescents 14 – 18 years, 3 times daily ½ teaspoon
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 Polish market in a category of “Pharmacopoeial products.”

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

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

Szadowska A. (1962) discussed Pharmacological investigation of extract of *Helichrysum arenarium*, conducted by Petrovski JA, Skokun WP, Turko IP, Farmakol. Toksikol., 16, 50, 1953 but there is no detailed information on this preparation from those times. The product has been present as first on the market in Russia and in Ukraine. The same publication was later cited by Turova AD & Sapozhnikova EN (1984). After Turova AD & Sapozhnikova EN (1984) the extract contained sum of 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 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 be increased to 0.1 g (two tablets) 2 – 3 times daily. The doses in children over 7 y.o. were the same. Therapy lasted 10 – 40 days. Currently according to database VIDAL-EKSPERT (www.webvidal.ru) Tipowaja kliniko-farmakologitcheskaja statja (typical summary of product characteristics) contain following medical data: *Pharmacological activities: Herbal preparation exhibiting bile secretion stimulatory, choleretic, cholekinetic, antiinflammatory, antibacterial, spasmolytic and wound healing activities.*

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

It stimulates the secretion of gastric juice and slows the function of its evacuation of the stomach and intestines, promotes improvement of 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 minutes before a meal (with a small amount of warm water), 1 tab. 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 AD & Sapozhnikova EN have described also the use of dry extract, *Extractum florum Helichrysi sicccum* in a form of granulated powder, it was used in a dose of 1g 3 times daily, during 2 – 3 weeks and 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 spoon (10ml) 3 – 4 times daily 15-20min before meals. There were used also a fluid extract *Extr. Helichrysi arenarii fluidum*, 3 times daily 1 teaspoon (5 ml) and herbal teas in a form of infusions; contained: Flor. Helichrysi arenarii 30.0 part and Herbae Absinthii, Fructus Foeniculi, Fol. Menthae pip. a.a. 20.0 parts.

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

Dry extract of Helichrysum (*Extractum florum Helichrysi arenarii siccum*) 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 2 - 3 weeks. (Turova AD & Sapozhnikova EN, 1984)

There were also used granules of Helichrysum flowers: 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 (100-125ml) 2 times a day, 30 minutes before meals.

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 tablespoon brewed with 2 cups of boiled water, 20 minutes, strain. Take 1/2 cup 3 times a day for 30 minutes before meals.

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.

There is a WHO Monograph Flos Helichrysii arenarii in *WHO monographs on the medicinal plants commonly used in the Newly Independent States (NIS). World Health Organisation 2010,* where as 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 a market as monocomponent herbal medicinal products, there are documented data on medicinal use of this herbal substance. Kažemekaitis A (2010) have compiled a historical data on the use of medicinal plant species

in Lithuania since 1873. From available tables it can be seen that 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 of 24th June 1938 on determination of prices in pharmacies.

The herbal substance has been contained in national monograph Species Cholagogae, placed in Regulation of Minister of Health from 5th of January 1949 about prices in Pharmacies, in a 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.

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, contained monograph for Inflorescentia Helichrysi and Species Cholagogae, where was contained: 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 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 W. (1955) in his manual of phytotherapy described two preparations: decoctions (10%) of Helichrysi flos, used as cholagogum in cholelithiasis and cholecystitis icterus, taken in single dose of 1 spoon (10 ml) every 2 hours and Extractum Helichrysi fluidum, taken 2-3 times daily a teaspoon (5 ml).

Sandy everlasting flower have been used in Germany.

According to Wichtl M (2002, 2004) text of the package insert of German Standard License (St. Zl. 1986, Publ. March 12, 1986) have contained 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 teaspoon (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 in 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 M, 2002; Blumenthal M, 1998).

There is a monograph in PDR for Herbal Medicine under commonly used in America name *Immortelle* (Gruenwald J, ed, PDR for Herbal Medicines, 2007).

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

Table 2: Overview of historical data

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Reference**
10% decoction Two preparations traditionally used in EU countries	used as cholagogum in cholelithiasis and cholecystitis icterus	10% decoction. taken in single dose 1 spoon (10 ml) every 2 hours.	Roeske W., 1955
Flavonoida florum Helichrysi arenarii [counted as a sum of 70% of flavonoids]. Available in a form of 50mg 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 y.o. were the same. Therapy lasted 10 – 40 days.	Turova A. D. & Sapozhnikova E.N., 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 1g 3 times daily, during 2 – 3 weeks	Turova A. D. & Sapozhnikova E.N., 1984
Extr. Helichrysi arenarii fluidum Preparation mentioned in Polish bibliography, but never been officially present on the market	In chronic liver inflammation diseases, gallbladder and biliary ways diseases	3 times daily 1 teaspoon (5 ml)	Turova A. D. & Sapozhnikova E.N., 1984
Decoctum Helichrysi Preparation present on the EU market	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 spoon (10ml) 3 – 4 times daily 15-20min before meals.	Turova A. D. & Sapozhnikova E.N., 1984

2.3. Overall conclusions on medicinal use

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

Table 3: Overview of evidence on period of medicinal use

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

3. Non-Clinical Data

There is no systematic 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 of flavonoid fraction from sandy everlasting and protective effects against acute ehanolic liver intoxication in rats were observed first by Jelinek in 1960. Fractions without flavonoids were free of giving this effect. In the same year Grzybowska isolated from sandy everlasting flower kaempferol-3-glycoside (astragalin), naringenin-5-β-D(-)–glycoside (helichrysin A) and naringenin-5-β-D(±)–glycoside (helichrysin B).

Szadowska A (1962) studied pharmacological effects of intravenous administration of the flavonoids (in dose 4mg/100g) versus positive control (Decholin, deoxycholic acid) and negative control (NaCl isotonic). Intravenous administration of kaempferol-3-glycoside and naringenin-5-glycoside to rats caused a 180-185% increase of bile secretion in compare to baseline (100%) after 15 min. (positive control decholine 294%, negative control NaCl - unchanged after 15 min.); apigenin administration - 160%. Comparison of reaction on apigenin versus reaction on ether extract (5mg/100g) 135% with max after 30 min indicated important role of ether soluble aglycones.

Administration of 10% decoction (1ml/100g) gave 156 % reaction; 10% infusion about 158% reaction; ethyl acetate extract and ethanol extract (50mg/100g) caused 138% and 135% reactions with max

after 15 and 30 min. Generally, after intravenous administration the max of activity appeared after 15 – 30 min. and lasted 60 – 75 min.

Investigations after duodenal administration to rats gave strongest reaction of positive control (Decholin solution), 240% after 15 min; 135% reaction of naringenin-5-glycoside and 130% reaction of kaempferol-3-glycoside after 60 min and no reaction of water and NaCl solution. Ethyl acetate extract caused 130% increase and ethanol extract about 135% increase; 10% infusion and decoction similar increase only by about 112% after 15 min. Apigenin 8mg/100g gave 150% reaction versus ether extract 125% reaction after 30 min. Max of activity appeared after 30 - 60 min. and lasted about 3 hours. The three flavonoids have pronounced choleretic activity.

Experiments on antispasmodic activity were conducted on smooth muscles, isolated from rabbits and rats intestines and on gall-bladders isolated from guinea pigs and rabbits. They have shown that apigenin in dissolutions 10^{-6} neutralized spasms induced by $BaCl_2$ in 50% and in dissolution 10^{-5} in 100%; kaempferol-3-glycoside in dissolution 10^{-4} in 30-40%; naringenin-5-glycoside in dissolution 5 x 10^{-3} neutralized in 90% spasm induced by $BaCl_2$ in dissolution 10^{-6}. Ether extract in dissolution 10^{-5} and ethyl acetate extract in dissolution 10^{-3} neutralized spasms induced by $BaCl^2$ in dissolution 10^{-4} in 25% and 40-70%. Ethanol extract in dissolutions 10^{-3} and 10^{-4} neutralized spasms induced by $BaCl_2$ in 100% and 25%. Decoction in dissolution 10^{-3} counteracted spasms induced by $BaCl_2$ in dissolution 10^{-5} in 75%. The strongest antispasmodic activity on smooth muscles and isolated gall bladders ex vivo possessed apigenin and ether extract, which contains mainly apigenin. Infusions and decoctions of sandy everlasting flower have weak spasmolytic activities.

All three flavonoids studied possessed spamolytic activities however the strongest was apigenin, weaker kempferol-3-glycoside and weakest naringenin-5-glycoside. In the studies there was observed relaxant activity, which was present already in the lowest tested concentration of extracts. Among extracts the strongest spasmolytic activity have ether extract, containing mostly apigenin, weaker ethyl acetate etract, containing naringenin-5-glycoside and kaempferol-3-glycoside and weakest was ethanolic extract. Extract without flavonoids was inactive. Infusion and decoction, apart from spasmolytic substances seemed to contain any spastic substances, this kind of activity was also detected in flavonoid free water extract. All tested flavonoids temporarily decreased blood pressure in dogs. Extract without flavonoids caused weak contraction of the intestinal muscles, which resolved after the administration of atropine. Generally it was observed clear choleretic activity of flavonoids, 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).

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

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 in vivo 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 Helichrysum arenarium, flos	1ml/100g; iv		158% after 15 min.	Mild choleretic

10% infusion of Helichrysum arenarium, flos		2ml/100g; id	112% after 15 min.	Very weak or no effect
10% decoction of Helichrysum arenarium, flos	1ml/100g; iv		156% after 15 min	Mild choleretic
10% decoction of Helichrysum arenarium, 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
Kaempferol-3-glycoside	4mg/100g; iv		180-185%	Mild choleretic
Kaempferol-3-glycoside		8mg/100g; id	130% after 60 min.	Mild choleretic
Dechol (deoxycholic acid) positive control	4mg/100g; iv		294% 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 bladers isolated from guinea pigs or rabbits

Herbal preparation or substance tested	Substance or preparation concentration	Experiment ex vivo, on gall bladers isolated from guinea pigs or rabbits		Main non-clinical conclusions
		Spasmolytic effect gall bladers isolated from guinea pigs [%]	Lowest spasmolytic concentration on gall bladers isolated from rabbits	
10% infusion or decoction of Helichrysum arenarium, flos	10^{-3} 10^{-3}	5 75		Mild spasmolytic
	10^{-3}		10^{-3} (80%-90%)	Weak spasmolytic
Ethanol extract (containing total flavonoid fraction)	10^{-3} 10^{-4}	100 15		Mild spasmolytic
	10^{-4}		4×10^{-3}	Weak spasmolytic
Ethyl ether fraction (containing apigenin)	10^{-5}	25		Mild spasmolytic
	10^{-6}		10^{-5}	Mild spasmolytic
Ethyl acetate fraction (containing glycosides of naringenin and kaempferol	10^{-3}	40 - 70		Mild spasmolytic
	10^{-4}		4×10^{-3}	Weak spasmolytic

Apigenin	10^{-6} 10^{-5}	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 90		Mild spasmolytic
	5 x 10^{-3}		2 x 10^{-3}	Weak spasmolytic
Kaempferol-3-glycoside	10^{-4}	25 – 30		Mild spasmolytic
	4 x 10^{-4}		10^{-4}	Weak spasmolytic
Water fraction	10^{-3} - 10^{-4}	- (Constriction)		Constriction
	10^{-4}		- (Constriction)	Opposite effect (constriction)

3.1.2. Secondary pharmacodynamics

Antioxidant activities and radical scavenging

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 antioxidant properties of its main phenolics, flavonoids (Czinner E et al. 1999). The authors studied the antioxidant properties of the lyophilized 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 lyophilized water extracts. The hydrogen-donating ability, reducing power property and total scavenger activity of the lyophilizate were determined using spectrophotometric and chemilumenescence methods. H-donor activity of the lyophilisate was determined to be more effective than silibinine but reducing power property and total scavenger capability were lower than that of silibilin. The flavonoid content determined in the lyophilisate was 0,47% and authors supposed that this concentration of flavonoids may be of therapeutic effect. The antioxidant properties of 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 have weak free radical scavenging activity in 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. Results were compared with the activity of the 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).

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 use of the extract as an alternative antioxidant for the food processing industries (Tepe B., 2004). Subfractions of dried methanolic extract from inflorescences of *Helichrysum arenarium*, obtained with ethyl acetate A, diethyl ether B, after alkaline hydrolyse C, were 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 Z. et al. 2004).
Albayrak S et al. (2010a, 2010b) investigated antiooxidant activity of plant material, of three subspecies of *Helichrysum arenarium* (L.) Moench: *erzincanicum* Davis & Kupicha, *rubicundum* (C.Koch.) Davis & Kupicha and *aucheri* (Boiss) Davis & Kupicha, in two complementary test systems, DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging and phosphomolybdenum assay. Plant material for study was collected in Turkey. The authors have used the whole overground plant parts, not only inflorescence. 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 indicate also large differences in phenolic compounds (ex. chlorogenic acid) between *Helichrysum arenarium* subspecies.

Antimicrobial activities
First investigations of antimicrobial activity of sandy everlasting flavonoids fraction were conducted in 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 µg/ml which is due probably mainly to the naringen (4', 5, 7-trihydroxyflavone). (Khristenko LA et al. 1977).

Antimicrobial activity of essential oil *Helichrysum arenarium*
Rančić A et al. (2005) investigated antimicrobial activities of 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. cladosporoides* 15/15, *P. funiculosum* 30/60, *T. viride* 10/15.
Sani AM (Sani AM, 2014) studied antimicrobial activities of essential oil distilled from over the 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 sterilized 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 390.625 – 6250 µg/ml. Essential oil distilled from the whole overground sandy everlasting plant may be different than from inflorescences.

Methanolic extracts

Albayrak S et al. (2010a, 2010b) studied antimicrobial properties of methanolic extract of the whole overground plant parts of three subspecies of *Helichrysum arenarium* (L.) Moench: *erzincanicum* Davis & Kupicha, *rubicundum* (C.Koch.) Davis & Kupicha and *aucheri* (Boiss) Davis & Kupicha, collected in Turkey. Determination of 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*. Methanolic extract from the whole overground sandy everlasting plant may have rather different qualitative content than from the inflorescence.

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

Appendino G et al. (2007) found that homoarenol (isolated under a name arzanol from *Helichrysum italicum*) inhibit HIV-1 replication in T cells and release proinflammatory cytokines in LPS stimulated primary monocytes. On the basis if the observation arzanol was identified as important antiviral component, studies of Bauer J et al. (2010) showed that it 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 PS et al. (2013).

Diuretic activity

Influence of flavonoids and extracts on urination was studied in rats and dogs. The investigated substances, flavonoids: kaempferol-3-glycoside, naringenin-5-glycoside and apigenin (10mg/100g) in 5ml of solution, extracts in water suspension, infusions and decoctions in water soluble form were administered to rats (150-210g). Control group obtained water. Urine volumes were monitored every 15 min, during 4 – 7 hours. No one of flavonoids nor extracts influenced urine elimination curve, in comparison with control group. (Szadowska, 1962). Decoction, infusion and various extracts of the dried herb of sandy everlasting (ether, ethanol, aqueous) were administered by the intraduodenally to dogs and via intragastric route to rats, at a doses of 10 mg/kg bw and 50 mg/kg bw, respectively. There was no diuretic activity of the extracts observed.

Hypotensive activity

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 WHO monograph (*WHO monographs on the medicinal plants commonly used in the Newly Independent* States, 2010) refers mainly to publication of Szadowska 1962 on the cholagogic and antispasmodic activities. The results of these studies justify the traditional 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 have shown apigenin and ethyl ether containing apigenin and other nonpolar aglycones. Last years important antiinflammatory activity of homoarenol/arzanol, present in extracts of sandy everlasting was confirmed, but the 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 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, 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 mutagenicity of flowers of Helichrysum arenarium (L.) Moench and its water extracts.

However Eroglu HE et al. 2010a in decoctions, prepared by boiling the whole aerial parts of *Helichrysum arenarium* (L.) Moench subsp. *erzincanicum*, growing in Turkey (4% w/v, 5 min.) found that the samples induced significant changes in micronuclei percentages, at concentrations of 0.5 mg/ml and 1 mg/ml. Water soluble factor present in the herb was not identified. This subspecies is known of high content of phenolic acids (specially chlorogenic acid, Albayrak S. et al., 2010a). It does not grew in Europe. Decoctions and methanolic extracts (10 g of the material in 100 ml) from of *H. arenarium* of subsp. *rubicundum* and *aucheri* did not induce changes in the frequency of micronuclei. Both decoction and methanolic extract of herb of *H. arenarium* subsp. *erzincanicum* influenced the replication index. Fractions or substances responsible for cytotoxicity of subspecies *erzincanicum* herb, were not identified. There were no observed effects of treatments with *H. arenarium* subsp. *aucheri* decoction and methanolic extract on mitotic index and on cellular proliferation in human lymphocytes. In the whole plant of other species *Helichrysum simillimum* DC, from South Africa, Elgorashi EE et al. 2008 observed mutagenic activity of extracts. The authors peformed separation procedure, monitored by Ames test and isolated kaempferol as a component responsible for mutagenic effect.

3.3.4. Carcinogenicity

There are no data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

Nor applicable.

3.3.7. Other special studies

Noe data available.

3.3.8. Conclusions

There are no pre-clinical data on reproductive and developmental toxicity. The results of 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 of *Helichrysum arenarium* (L.) Moench, flos.

3.4. Overall conclusions on non-clinical data

Available non-clinical data are based mainly on published results of studies, handbooks and WHO monograph. The data include results of tests of 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 indicate mild bile excretion promoting activity. In the experiments it has been compared to 1/3 activity of deoxycholic acid. The second group of tests are studies on influence of upper mentioned extracts and substances on spasmolytic/antismasmodic activity of isolated guinea pigs and rabbits gallbladders and rabbits and rats bowel sections. The results of the experiments indicate 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 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

There are no dose response data available.

4.2.2. Clinical studies (case studies and clinical trials)

There are no available results of clinical trials.

In old Russian bibliography there were publications about clinical observations of gallbladder treatment with orally applied sandy everlasting herb and extract and on experience in use of sandy everlasting preparations in treatment of chronic cholecystitis and liver and gall ways inflammatory diseases. (after Turova 1984).***Clinical studies in special populations (e.g. elderly and children)***

Not applicable

4.4. Overall conclusions on clinical pharmacology and efficacy

Human clinical observations of sandy everlasting preparations are restricted to very old publications. The observations were conducted on patients with inflammatory diseases of biliary system, cholecystitis, cholangitis, hepato-bliliary diseases and dyskinesis. However, the use of the products in these indications in Eastern European countries is documented until today, 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 recorded 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 was about 170000 package units of products per year in turnover, containing *Helichrysum arenarium* (L.) Moench, flos, what correspond to about 1490000 of daily doses of the products. Combination product containing ethanolic extract of sandy everlasting flower is commonly used in Poland. According to its last PSUR adverse reactions were not recorded in years 2008-2011. The product was used in year 2013 at the level of 1.299 mln patient days. This year, herbal teas were used on the market in Poland at the level of 692000 patient days and in Lithuania 30000 patient days. 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, any adverse reactions have not been recorded.

5.4. Laboratory findings

No data available

5.5. Safety in special populations and situations

Data on special populations are not available.

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

Hypersensitivity for herbal substance. Asteraceae (Compositae) family. Biliary tract blockage.

5.5.3. Special Warnings and precautions for use

Because of lack of data the use for children under 12 years of age is not recommended.

5.5.4. Drug interactions and other forms of interaction

Not known.

5.5.5. Fertility, pregnancy and lactation

No fertility data available.

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

5.5.6. Overdose

Overdose have 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 of Asteraceae family. Safety during pregnancy and lactation have 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 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 one of the preparations have been used for many decades. Among countries of European Union Inflorescentia Helichrysi was introduced to Polish Pharmacopoeia in 1954. A medical tradition in 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 ben 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. On a base of long tradition, the medicinal use of herbal teas of sandy everlasting flower for relief of symptoms of digestive disorders with sensation of fulness, bloating and flatulence, could be regarded as plausible.

Because of 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, what 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