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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Menyanthes trifoliata* L., folium

Draft

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Menyanthes trifoliata* L., folium (bogbean leaf)
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Liquid extract (DER 1:1) extraction solvent ethanol 25% (V/V) d) Tincture (1:5), extraction solvent 45% ethanol (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea Herbal preparations in liquid or solid dosage forms for oral use
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Menyanthes trifoliata* L., folium. 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(s)

Bogbean leaf, (Eur Pharmacopoeia No:1605, *Menyanthidis trifoliatae folium*) consists of dried, entire or fragmented leaves of *Menyanthes trifoliata* L. with very bitter and persistent taste (required bitterness value min. 3000) and showing a presence of loganin in thin layer chromatography.

Constituents: (Steinegger & Weibel 1951, Krebs 1957, 1958, Battersby 1968; Rułko 1969, Ciaceri 1972; Mel'chakova 1976, Świątek et al. 1986; Steinegger & Hansel 1988, Junior 1989, Hegnauer 1990; Adamczyk 1990; Wagner & Bladt 1996, Blaschek 1998; Wichtl 1984, 2004, ESCOP 2013)

Iridoids: secoiridoid glycosides: dihydrofoliamenthin, foliamenthin, menthiafolin and smaller amounts of **iridoid glycosides** loganin and sweroside. The total amount of bitter substances is referred to be approx. 1%.

Flavonoids: Flavonol kaempferol, isorhamnetin, quercetin and their glucosides hyperoside, rutoside and trifolin (kaempferol-3-O-galactoside).

Coumarins: (in leaves) scopoletin, scoparone, braylin.

Phenolic acids: chlorogenic, caffeic, ferulic, sinapic, vanilic and protocatechic.

Triterpenoid substances: small amounts of lupeol, beta-amyrenol, betulin, betulic acid

Sterols (α-spinasterol).

Other constituents such as: ascorbic acid, tannins, polysaccharides.

Small amounts of alkaloids (in leaves): gentianine, gentianidine, gentialuteine are considered to be artefacts of the ammonia used in the isolation procedure.

Herbal preparation(s):

a) Comminuted herbal substance

b) Powdered herbal substance

c) Liquid extract (DER 1:1) extraction solvent ethanol 25% (V/V)

d) Tincture, (1:5), extraction solvent 45% ethanol (V/V)

Tinctura Amara in Pharmacopoea Bohemoslovenica (1947b, 1987) and in Pharmacopoea Polonica (1954b, 1970b, 2002b) contained bogbean leaf and currently, the Tinctura Amara is still a component of combination products *Guttae stomachicae* distributed in Poland.

Combination herbal granulate manufactured in Poland in years 1967-2000 contained *Menyanthidis folium.*

Multi-component bitter tinctures containing bogbean leaf are used in Hungary and Austria.

Analytical marker

Loganin has been established as analytical quality marker by the European Pharmacopoeia (Eur Pharm:1605) for *Menyanthidis trifoliatae folium*.

1.2. Search and assessment methodology

The area of search for data on the medicinal use of bogbean leaf or its preparations covered: pharmacopoeias, medical and pharmaceutical manuals and books of the area of pharmacognosy and on its medicinal use. Some old books were found in a digital version in libraries as a result of the extensive use of search engines; they were used online.

Searching for with the use of search engines mentioned below was performed online in the area of medical databases which include data from scientific and medical press.

The subject of searching for were: books, book chapters, articles and letters in journals. The acts of law and regulations concerning approving the herbal substances and preparations to the market were taken into account. (See the list of references in Annex)

Search engines used: Google, Google Scholar, Bing.

Scientific databases: EBSCOhost, ScienceDirect, SciFinder, Scopus, Wiley, Reaxys (chemical database), ProQuest (academic resources).

Medical databases: Access Medicine, Embase, Medline complete, PubMed, The Cochrane Library, UpToDate, Polska Bibliografia Lekarska.

Toxicological databases: Toxline (since 2019 as TOXNET included into PubMed), LiverTox (in Bookshelf), FDA Poisonous Plant Database, GENE-TOX (since 2019 passed to the PubChem).

Pharmacovigilance resources: EudraVigilance database and WHO database were searched for data on Menyanthes trifoliata, folium, preparations. There were no adverse events recorded for single component products authorized as well-established use products, registered as traditional herbal medicinal products nor registered in EU countries on a basis of national law.

Data from EU and non-EU regulatory authorities: Data on Licensed Natural Health Products Database (LNHPD) were available from Health Canada.

Other resources: No available data

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

The information is mainly based on data obtained from the National Competent Authorities on documents on information exchange (EMEA/HMPC/137093/2006) however information on one combined product containing bogbean leaf, was found in its Summary of Product Characteristics, what is available in the web-page of the National Competent Authority.

Information on medicinal products marketed in the EU/EEA

In March 2018 a request was sent for information on marketed products containing *Menyanthidis trifoliatae folium* to the member states. From CZ, H, NL, D, SV, LV information was obtained. According to the information only in Poland mono-preparations containing *Menyanthes trifoliata* L., folium, are currently on the pharmaceutical market. Data on officinal formulas are available from CZ and PL. Data on combination products are available from H and A. The data on herbal medicinal products which were been approved, registered or authorised for marketing are summarized in Table 1.

Table 1: Overview of data on marketed medicinal products

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Menyanthidis folium	Stimulation of hunger in lack of appetite.	Herbal tea, infusion. 1 teaspoon (1.3 – 1.6 g) of leaves pour with a cup of boiling water (150 ml) for 10 - 15 min., strain and drink warm infusion 1 – 3 x daily. SD range 1.3 - 1.6 g DD range 1.3 - 4.8 g	*Liść bobrka*. Authorization confirmation Nr 5146, 10.05.1993
Menyanthidis folium	Supplementary for stimulation appetite	Herbal tea, infusion/decoction 1 teaspoon (2.0 g) pour with boiling water, boil 5 min. under cover, stay for 10 min., strain. Drink a ¾ glass (150 ml, corresponding 1.5 g) of the prepared herbal tea, 2 – 3 times a day, 30-60 min. before meals. SD 1.5g DD 3.0 - 4.5g	*Liść bobrka*. Registration Certificate IL-3334/LN 1992.09.21

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

Austria

Bogbean leaf is contained in two traditional multi-component liquid extracts used in dyspepsia. Product 1 contains in 100 ml the equivalent of 53 mg *Menyanthidis folium*; product 2 contains in 100 ml the equivalent of 12 mg *Menyanthidis folium*.

Great Britain

Combination product containing 7.5 mg of *Menyanthes trifoliata* L., herb, dry extract, Guaiacum resin, celery fruit extract and dandelion root extract.

Hungary

Two multi-component products containing 8 g of liquid extract (1:10) from the mixture of herbal aromatic and bitter substances, among them of *Menyanthidis folium*.

Poland

Combination products *Tinctura Amara*

The Tinctura Amara, and later named Amara Tinctura, was been further combined in equal parts of *Valerianae tinctura*, *Menthae piperitae tinctura*, and *Hyperici tinctura* and manufactured as several products authorised/registered in Poland under the names *Guttae stomachicae*.

5 combination products containing: *Valerianae tinctura* 25%; *Menthae piperitae tinctura* 25%; *Amara tinctura 25%*, *Hyperici tinctura* 25%, manufactured by different producers are present on the market.

Herbal granulate containing *Foenugraeci semen* 20 parts, *Salviae folium* 17 p., *Agrimoniae herba* 10 p., *Menyanthidis folium* 7 p., *Hyperici herba* 7 p., *Glycyrrhizae radix* 3 p., *Levistici radix* 3 p., *Menthae piperitae aetheroleum* 0.1 p.

Officinal formulas

However *Menyanthes trifoliata* L., folium, has been traditionally used in EU countries and outside EU, it was also been used in **combinations products** which were been in use as officinal drugs: herbal tea combinations in a form of infusion, combined tinctures or oral liquids.

Frerichs (1938b) in Hagers Handbuch tabled pharmacopoeal combination formulas containing bogbean leaf, under a name of Species amarae or Species amaricantes, from pharmacopoeas of Austria, Croatia, Switzerland, Hungary, Netherlands and Denmark. According to the source (1938c) *Menyanthidis trifoliatae folium* (*Folia Trifolii*) were used in herbal tea combinations in pharmacopeias: Austrian, Croatian, Helvetic, Hungarian, Nederlands and in Denmark.

In Pharmacopoea Polonica II (1937) and III (1954) Species amarae contained *Folium Menyanthidis* 20 p for 100. In Pharmacopea Polonica V Suppl. I (1995b) and VI (2002c) bogbean leaf was included in the Species stomachicae, containing *Menyanthidis folium* 25 p. for 100.

In Pharmacopoea Bohemoslovenica ed. II (1954) Species amaricantes contained *Folium trifolii fibrini* (*Menyanthidis trifoliatae folium*) 15 g for 100. .

Other commonly used officinal drugs were combination tinctures which were used under a name of Tinctura Amara. In Pharmacopoea Bohemoslovenica I (1947) it contained *Folium Menyanthidis* 20 g for 100. In Pharmacopoea Bohemoslovenica IV, (1987) Tinctura amara contained: *Folium trifolii fibrini* (*Menyanthidis trifoliatae folium*) 20.0 g, together with *Herba absinthii, Pericarpium aurantii dulce, Radix gentianae,* and *Oleum cinnamomi*. In Pharmacopoea Polonica III (1954) Tinctura amara was made of: *Folium Menyanthidis* together with *Radix Gentianae, Herba Centaurii, Exocarpium Aurantii amari, Rhizoma Calami* and *Herba Absinthii*.

Other products

Hungary

2 products containing tincture (4.8 g in 100 ml of product) of 22 herbal substances (one of 5 bitter ingredients are *Menyanthes trifoliata* leaves), have been on the market since 1998, classified as 'healing products' used for treatment of mild digestive disorders such as a feeling of bloating and fullness, constipation, biliary problems and lack of appetite.

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

In the United States of America (USA) *Menyanthes trifoliata* leaves (named there as bog bean) are known to be used in the indications approved by the German Commission E: in dyspeptic complaints and in loss of appetite. Single doses are 0.5 -1.0 g (1 teaspoon is estimated to contain about 0.9 g) in a form of decoction which is prepared by pouring the mentioned quantity of the herbal substance with cold water and bringing it rapidly to boil (it is named infusion). The ½ cup of the prepared decoction is taken before each meal (Gruenwald 2004).

According to the database on Licensed Natural Health Products Database (LNHPD) from Health Canada, there are two licensed products containing bogbean leaves preparations there. Liquid extract (1:5) prepared with ethanol-water (of unknown concentration), with posology in adults: teaspoon (2.5 ml) used 3 times a day. Indication: to help relieve rheumatic pain. The second product is called tincture, contains extract (1:3) prepared with ethanol-water of unknown strength. It is used in adults in a single dose of 2 ml 3 times daily. Indications: *Traditional herbal medicine to help relieve rheumatism pain*. Moreover in Canada are used herbal tea combinations containing *Menyanthidis folium*, one to reduce rheumatic pain and as a digestive tonic and four other herbal tea combinations where *Menyanthes trifoliata* was declared as one of the active components are used to help digestive complaints, to stimulate appetite and as a diuretic.

There were several historical medical records from XIX century in Russia reviewed on Henriette's Herbal Homepage (Menyanthes. – Buckbean [1]): https://www.henriettes-herb.com/eclectic/kings/menyanthes.html. *Folia Menyanthidis trifoliatae* were present in editions of Russian Pharmacopoeia (Shikov, 2014). Bogbean leaves were used as a bitter agent for stimulation of appetite and for intensify intestinal secretion in cases of gastritis with hypoacidity and also as cholagogue. It was commonly used in a form of infusion/decoction made of one spoon in a glass of boiling water (200 ml), boiled 5 minutes, for 1-2 hours and used 5 - 10 min before meals, 3 times a day. There was also used herbal tea combination of *Menyanthidis folium* with *Absinthii herba* 15 + 15 g for infusion as a tea and the tea was used in a dose of 1 spoon, 2 – 3 times a day, 15 – 20 min before meals (Turova & Sapozhnikova 1984).

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

Bogbean leaf has been used in many European Union countries during several decades. Frerichs in Hagers Handbuch in the monograph for Menyanthes (1938a) mentioned *Folia Trifolii fibrini* being known in Germany as Bitterklee, Bogbean (buckbean) leaves in Britain and *Feuilles de menyanthe* (*Feuilles de trefle d'eau*) in France. *Menyanthes trifoliata* L., folium was regarded as typical bitter agent recorded by many European national pharmacopeias as officinal (Roeske 1955). *Herba Trifolii aquatici s. fibrini* of species Menyanthes trifoliata was included in the first Polish national pharmacopeia (Pharmacopoeia Regni Poloniae 1817) with the following description: *Planta perennis palustris Poloniae: Herba amara, foliis ovatis, ternis*. Later only leaf was in use and present in Farmakopea Polska (Pharmacopoea Polonica) IInd edition (1937), IIIrd edition (1954), IVth edition (Vol. II, 1970) as *Folium Menyanthidis*, in VIth edition (2002) as *Menyanthidis folium* and since VIIIth until today's XIth edition (2017) is named *Menyanthidis trifoliatae folium*. *Menyanthidis folium* was present also in the first Czechoslovak pharmacopoea (Pharmacopoea Bohemoslovenica 1947). It was also been known for its use in Latvia (Rubine 1977). In Poland, the comminuted herbal substance was been used as herbal tea and since the fifties to seventies was prepared as a decoction (Gobiec & Konieczny 1967, Bobowska 1977), then as decoction or infusion (Ożarowski 1976), and last 30 years as the infusion. Now herbal tea, infusion, is the only form present on the EC pharmaceutical markets (see below Table 1). However, on a base of data from EC countries, there is no one single (mono-component) product registered or authorized on a base of Directive 2004/24, containing sole *Menyanthes trifoliata*, folium preparation. The products which have been present on a market were licensed before the accession to the European Union.

In classical manuals of phytotherapy bogbean leaf is referred to be a simple bitter (*amara pura*), with bitterness value between gentian and centaury (Schulz & Hänsel 2004).

[1] Buckbean is an old common name of Menyanthes trifoliata L. In this document it is used a name bogbean, according to the European Pharmacopoeia and the British Herbal Pharmacopoeia.

In the British Herbal Pharmacopoeia and in its consolidated version (1976, 1983) was a monograph Menyanthes on the use of its preparations: dried leaves in a form of herbal tea, infusion; liquid extract (1:1) in 25% alcohol and tincture (1:5) in 45% alcohol (see in Table 2). Action: Bitter, Diuretic. Indications: Rheumatism, Rheumatoid arthritis. Specific indications: Muscular rheumatism associated with general asthenia. This tradition is different than in continental Europe countries.

The powdered herbal substance was documented by the bibliography to be used in adults and children as officinal drugs, prepared mainly in dosage forms available in pharmacies (wafers, capsules) in single doses for adolescents and adults between 0.5 - 3.0 g (Roeske 1955, Ożarowski 1976) and in children administered, with milk or water, in a dose of 0.3g (Olechnowicz-Stępień 1986).

Soft water extract of leaves was also been used in Poland and Germany. *Extractum Menyanthidis* (Pharmacopoea Polonica II 1937c) (DER 1:2) extraction solvent boiling water, after water evaporation, presented sticky substance which was used especially for preparation of bitter pills. It was noted also by Frerichs in Hagers Handbuch (1938a) in a monograph for Menyanthes. However, it was not included in the further edition of Polish pharmacopoea (FP III 1954) and the use of the preparation disappeared in next decades.

Liquid extract, DER (1:1), extraction solvent 25% ethanol (BHP 1983; Newall 1996, Barnes et al. 2012), have been used in Britain.

Tincture, DER (1:5), extraction solvent 45% ethanol (BHP 1983; Newall 1996, Barnes et al. 2007), which have been used in Britain.

Table 2: Overview of historical data (with data on formerly registered medicines)

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use Single doses (SD) and daily doses (DD) counted as herbal substance**	**Reference**
Comminuted herbal substance for herbal teas			
	Lack of appetite, digestive disturbances		
Folium Menyanthidis, comminuted herbal substance for herbal tea, infusion	Lack of appetite, digestive disturbances, gastrointestinal tract atony, insufficient bile excretion.	Infusions: 10.0 - 20.0 g in 200 – 250 ml of water. Posology: 10 ml (one tablespoon) of the prepared infusion 2 – 4 times daily[2] Strength: 0.4 – 0.5 g/10 ml [= 6.0 – 7.5 g/150 ml] SD 0.4 – 0.5 g; DD 0.8 - 2.0g	*Urzędowy Spis Leków* (Official Register of Drugs in Poland) 1950. Informator Terapeutyczny USL (Therapeutic Handbook for Official Register of Drugs) 1955, 1959

[2] When 20 g of the herbal substance is used for infusion a half of it is absorbed by the herbal substance and lost removed by the straining, and only a half (100 ml) is adjusted with boiling water to the 200 ml volume and further used for dosage during the day. The prepared infusion after the filtration and adjustment of water correspond to 10 g of the herbal substance. When 250 ml is used for infusion a 100 ml is absorbed and 150 ml is further adjusted to the 250 ml volume and used for dosage during a day.

	Also in neurasthenia and neuralgias		As above
Folium Menyanthidis, comminuted herbal substance for herbal tea infusion or decoction	Dyspepsia, hypoacidosis, lack of appetite, intestine atony, weakening of digestive function	Infusion or decoction 4.0 g in 200 ml. Taken with spoons (at least 20 ml of the infusion) what correspond to at least 0.4 g of herbal substance); 4 – 5 times daily, 30 min. before meals. Strength: 0.4 - 0.6 g/20 - 30 ml [= 3.0 g/150 ml] SD 0.4 - 0.6 g; DD 1.6 - 3.0 g	Ożarowski 1976
Folium Menyanthidis, comminuted herbal substance for herbal tea, infusion	Oral use: For the stimulation of appetite, stimulation of digestive and bile secretion	Infusion of 1-2 teaspoons (1.3 - 2.6 g) per cup of boiling water. Drink a ¼ cup (50 – 60 ml) 30 minutes before a meal. Strength: 0.32 – 0.65 g/50 – 60 ml [= 1.3 - 2.6 g/150 ml] SD 0.32 – 0.65 g; DD 1.3 – 2.6 g	Rubine et al. 1977
*Folium Menyanthidis,*comminuted herbal substance for herbal tea, infusion	Oral use: for gastritis and ulcers. Comment *of Rapp* : Not plausible for traditional use, without medical consultation	Infusion of 1-2 teaspoons (1.3 -2.6 g) per cup of boiling water. Drink a ¼ cup (50 – 60 ml) 30 minutes before a meal. Strength: 0.32 - 0.65/50 – 60 ml [=1.3 - 2.6 g/150 ml] SD 0.32 – 0.65 g; DD 1.3 – 2.6 g	Rubine et al. 1977
Folium Menyanthidis, comminuted herbal substance for infusion or decoction	In weakened secretory function of the stomach, hypoacidosis.	Infusion or decoction of a ½ spoon (2.2 g) of the herbal substance to a glass of water (200 – 250 ml). The infusion use 4 – 5 times a day 60 - 30 min before a meal. Strength: 0.4 - 0.5 g/40 – 50 ml [= 1.3 – 1.6 g/150 ml] SD 0.4 - 0.5; DD 1.6 - 2.5 g	Ożarowski et al. 1978
		Adults and adolescents: SD range 0.3 - 1.0 g DD range between 0.8 g (2 x 0.4 g) - 3.0 g	
Herbal tea, decoction	Used as a bitter to stimulate the appetite and the secretion of gastric juice	Herbal tea, infusion or decoction, made by the pour of 0.5 – 1 g of comminuted herbal substance by the cold water, than heating decoct briefly and after 5 - 10 min. pass through a tea strainer. Drink a cup (150 ml) of the unsweetened infusion or decoction ½ hour before meals. 1 teaspoon = about 0.9 g[3]. Strength: 0.5 - 1.0 g/150 ml SD 0.5 - 1.0 g; DD 1.5 - 3.0 g	Wichtl M 1984
	In minor articular and muscular pain.		

[3] 0.9 g correspond to the level teaspoon, see also estimations below the Table.

Folium Menyanthidis, comminuted herbal substance for herbal tea, infusion	Adults. In minor articular and muscular pain.(See explanations below the Table) In original: *(Action: Bitter, Diuretic. Indications: Rheumatism, Rheumatoid arthritis. Specific Indications: Muscular rheumatism associated with general asthenia.)*	Herbal tea, infusion. 1 - 2 g for one cup of infusion (150 ml). SD 1.0 - 2.0 g; DD 3.0 - 6.0 g	British Herbal Pharmacopoeia 1983, Newall CA et al.1996, Barnes J et al. 2007
		Adults: SD 1.0 - 2.0 g DD 3.0 - 6.0 g	
Comminuted and powdered herbal substances			
	Dyspepsia, Lack of appetite		
Folium Menyanthidis, powdered	Dyspepsia, hypoacidosis, lack of appetite, intestine atony, weakening of digestive function	Adults: Wafers, capsules. Single dose 0.5 g used 2 – 4 times daily. SD 0.5 g; DD 1.0 - 2.0 g	Ożarowski 1976
Powdered herbal substance	Lack of appetite in children Comment: The age proposed to be accepted by MLWP only over 12 years	Children, Adolescents: Single dose: ¼ teaspoon (0.3 g) of powdered herbal substance SD 0.3 g; DD 1.2 g	Olechnowicz-Stępień 1986, 1992
		Adolescents, Adults: SD range 0.3 – 0.5 g DD range 1.0 - 2.0 gange 1.0-2.0	
	In minor articular and muscular pain		
Dried leaves, comminuted/powdered	Adults. In minor articular and muscular pain. In original: (*Action: Bitter, Diuretic. Indications: Rheumatism, Rheumatoid arthritis. Specific Indications: Muscular rheumatism associated with general asthenia*.)	Dried powdered leaves (capsules) taken in a dose of 1-2 g thrice daily SD 1.0-2.0g; DD 3.0-6.0g	British Herbal Pharmacopoeia 1983
		Adults: SD 1.0 - 2.0 g; DD 3.0 - 6.0 g	
Liquid extracts	***In minor articular and muscular pain***		
Liquid extract DER (1:1) extraction solvent ethanol 25% (v/v)	Adults. In minor articular and muscular pain. In original: (*Action: Bitter, Diuretic. Indications: Rheumatism, Rheumatoid arthritis. Specific Indications: Muscular rheumatism associated with general asthenia*.)	Single dose 1 - 2 ml. Used thrice daily. Duration of use not restricted. SD 1.0 - 2.0 g; DD 3.0 - 6.0 g	British Herbal Pharmacopoeia 1983, Newall CA et al. 1996, Barnes J et al. 2007
Tincture (1:5), extraction solvent 45% ethanol (v/v)	Adults. In minor articular and muscular pain. In original: (*Action: Bitter, Diuretic. Indications: Rheumatism, Rheumatoid arthritis. Specific Indications: Muscular rheumatism associated with general asthenia*.)	Single dose 1 - 3 ml. Used thrice daily. Duration of use not restricted. SD 1.0 - 3.0 g; DD 3.0 - 9.0 g	British Herbal Pharmacopoeia 1983, Newall CA et al. 1996, Barnes J et al. 2007
		Adults:	

		SD range 1.0 - 3.0 g DD range in adults 3.0 - 9.0 g	

On a base of contemporarily used spoons and teaspoons in this table are estimated average medium contents of Menyanthidis trifoliatae folium, comminuted herbal substance: full spoon 5.3 +/- 0.6 g; medium spoon 4.5+/-0.3 g; full teaspoon 1.6+/-0.1 g; medium teaspoon 1.3+/-0.1 g.

In a first half of 20th century bogbean leaf was used in a form of strong bitter tea infusions, prepared once for a day and taken in a relatively small single doses of 10 ml (1 spoon). For this way of use the infusion was prepared of 10 – 20 g of the herbal substance in 200 – 250 ml of boiling water (Farmakopea Polska III), and kept for use during a day in a thermo-isolated vessel. With daily use of 2 – 4 single doses only 20 - 40 ml was taken of the portion prepared for a day (Informator Terapeutyczny USL 1955, 1959). However the volume of the preparation was small but its concentration and bitter value was high. The way of tea preparation, for its use during a day in a divided doses was common, although in the seventies the single doses have bigger volume of 20 – 60 ml (Ożarowski 1976; 1978; Rubine 1977). In Poland traditionally were prepared infusions/decoctions of 200 – 250 ml (1 glass) water.

2.3. Overall conclusions on the medicinal use

The powdered herbal substance was bibliographically documented to be used in adults and children as officinal drugs, prepared in dosage forms available in pharmacies. They are generally exempted from registration on a base of art. 3, par. 1 and 2 of Directive 2001/83.

Herbal teas have been used traditionally in two kinds of indications. In continental Europe, the main indications were: temporary loss of appetite (for stimulation of gastric juice and bile secretion) and for the relief of mild digestive disorders such as bloating and flatulence. There is bibliographic evidence for using smaller doses of bitter infusions in school-age children, however it is proposed by HMPC to limit the use of the products only to adults, as in other bitter substances monographs.

The tradition of use tinctures (1:5) with extraction solvent ethanol in concentrations 45% (V/V) is documented by bibliography both in lack of appetite and minor articular or muscular pains.

The tradition of use of liquid extract (DER 1:1) with extraction solvent ethanol 25% (V/V) in minor articular and muscular pains are also documented by the below-tabeled bibliography.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Strength Posology**	**Period of medicinal use**
	Mild dyspeptic or gastrointestinal disorders / Temporary loss of appetite		
Folium Menyanthidis, Herbal tea, infusion or decoction	Adolescents, Adults. Lack of appetite. Weakened secretory (hypoacidosis) and digestive function of the stomach (dyspepsia).	Infusion/decoction of 2.2 - 4.0 g herbal substance in 200 ml [corresponding to 1.6 - 3 g/150 ml] used in single doses 40 – 50 ml, taken 4 – 5 times daily, 30 min. before meals. SD 0.4 g - 0.6 g; DD 1.6 - 3.0 g	Ożarowski 1976; Ożarowski et al. 1978

Herbal preparation Pharmaceutical form	**Indication**	**Strength Posology**	**Period of medicinal use**
Menyanthidis folium, herbal tea, infusion	Adolescents, Adults. in lack of appetite.	Herbal tea, infusion. 1 teaspoon (1.3 – 1.6g) of leaves pour with a cup of boiling water (150 ml) for 10 - 15 min., strain and drink warm infusion 1 – 3 x daily. Strength: 1.3 - 1.6 g/150 ml SD range 1.3 - 1.6 g; DD range 1.3 - 4.8 g	Liść bobrka. Authorization confirmation Nr 5146, 10.05.1993
Menyanthidis folium, herbal tea, infusion	Adolescents, Adults. Supplementary for stimulation appetite	Herbal tea, infusion. 1 teaspoon declared to be 2.0 g pour with boiling water, boil 5 min. under cover, stay for 10 min., strain. Drink ¾ glass (150 ml, corresponding 1.5 g) of the prepared decoction, 2 – 3 times a day, 30 - 60 min. before meals. Strength: 1.5 g/150 ml SD 1.5 g; DD range 3.0 - 4.5 g	Liść bobrka. Registration Certificate IL-3334/LN 1992.09.21
Menyanthidis folium, Herbal tea, infusion		Strengths equivalent to: 1.3 – 3.0 g/150 ml SD range 0.4 – 1.6 g DD range 0.8 – 4.8 g	
Menyanthidis trifoliatae herba Herbal tea, decoction	Used as a bitter to stimulate the appetite and the secretion of gastric juice	Herbal tea, infusion or decoction, made of 0.5 – 1g of comminuted herbal substance, used in both indications, 3 times a day ½ hour before meals. Strength: 0.5 - 1.0 g/150 ml SD range 0.5 - 1.0 g; DD range 1.5 - 3.0 g	Wichtl 1984
Folium Menyanthidis, powder	Adults. Dyspepsia, hypoacidosis, lack of appetite	Capsules, wafers containing powdered herbal substance in single dose 0.5 g. Used 2 – 4 times daily. SD 0.5 g DD 1.0 - 2.0 g	Ożarowski 1976
	Minor articular and muscular pain.		
Folium Menyanthidis, powder	Adults. In minor articular and muscular pain.	The powdered herbal substance in capsules used in single dose 1 – 2 g, thrice daily. SD range 1.0 - 2.0 g; DD range 3.0 - 6.0 g	British Herbal Pharmacopoeia 1983.
Folium Menyanthidis, herbal tea, infusion	Adults. In minor articular and muscular pain.	Herbal tea, infusion. 1 - 2 g for one cup of infusion (150 ml). Used thrice daily. Duration of use not restricted. Strength: 1 – 2 g/150 ml SD range 1.0 - 2.0 g; DD range 3.0 - 6.0 g	British Herbal Pharmacopoeia 1983.

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Tincture, DER (1:5), extraction solvent 45% ethanol (v/v)	Adults. In minor articular and muscular pain.	Single dose 1-3 ml. Used thrice daily (DD 3 – 9 ml). Duration of use not restricted.	British Herbal Pharmacopoeia 1983
Liquid extract DER (1:1) extraction solvent ethanol 25% (v/v). Oral liquid	Adults. In minor articular and muscular pain.	Liquid extract (1:1) in single dose 1-2 ml. Used thrice daily (DD 3 – 6 ml). Duration of use not restricted.	British Herbal Pharmacopoeia 1983.

Indications

According to the market and literature overview bogbean leaf preparations fulfills the criteria of traditional medicinal use throughout at least 30 years including 15 years of tradition within the European Union countries in the following indications:

Indication 1

- Traditional herbal medicinal product used in temporary loss of appetite

Indication 2

- Traditional herbal medicinal product used for the relief of mild digestive disorders such as bloating and flatulence

Indication 3

- Minor articular and muscular pain.

Posologies

Indication 1) and 2)

Adults

a) Herbal teas

a1) Herbal tea: 0.4 – 1.6 g of the comminuted herbal substance in 150 ml of boiling water as herbal tea infusion used 2 - 4 times daily, in Indication 1) 30 min. before meals, in Indication 2) between meals.

Daily doses: 0.8 – max. 4.8 g

Indication 1)

a2) Herbal tea: 0.5 – 1.0 g of the comminuted herbal substance in 150 ml of water as infusion or decoction used 3 times daily, 30 min. before meals.

Daily doses: 1.5 g to 4.5.g.

Adults

b) Powdered herbal substance in single dose 0.5g, 3 - 4 times daily.

Daily dose 1.5 - 2.0 g

Indication 3)

Adults and Elderly

a) Herbal tea: 1 - 2 g of the comminuted herbal substance in 150 ml of boiling water as infusion, used 3 times daily

b) Powdered herbal substance in single doses 1 – 2 g, 3 times daily

c) Liquid extract (DER 1:1) extraction solvent ethanol 25% V/V

Single dose 1.0 – 2.0 ml, 3 times daily

e) Tincture, (DER 1:5), extraction solvent 45% ethanol V/V

Single dose 1.0 – 3.0 ml, 3 times daily

3. Non-Clinical Data

Non clinical data on bogbean leaf or its extracts are not available

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

3.1.1. Primary pharmacodynamics

There is no systematic data on the primary pharmacodynamics of the bogbean leaf, connected with its use in traditional indications.

Digestive stimulation

For the view on the activity of Menyanthes trifoliata preparations, important are available results of works on loganin, the bitter compound of the leaves both stimulating digestive functions (Takeda et al., 1980) and exhibiting some protective effects on liver and pancreas, (Kim et al. 2005 Park et al. 2011, Yamabe et al. 2010).

Antiinflammatory activity

There are limited *in vitro* screening data showing mild inhibition of prostaglandin biosynthesis and weak antiplatelet activity by the lyophilized Menyanthes trifoliata leaves water extracts, which were reported to be used in Sweden (Tunón et al. 1995).

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

Herbal preparation tested	**Strength Dosage Route of administration**	**Experimental model In vivo/ In vitro**	**Reference Year of publication**	**Main non-clinical conclusions**
Loganin, Loganin aglycone	Loganin and loganin aglycone solutions administered iv, in doses 25 mg/kg and 50 mg/kg	In vivo. Anesthesized male Wistar rats (200-250g); administered with iv with single doses of the tested substances. Bile volume collected at 30 min intervals via common bile duct caniules.	Takeda et al. 1980	Important growth of bile secretion by loganin aglycone in the tested doses
Comparable/similar preparations to preparations of the monograph Menyanthes trifoliata, leaves, two-step water extracts	Water (20°C) two-step extract, (1:20) and (1:10) combined and lyophilized	Antiplatelet activity. In vitro model of PAF induced exocytosis test	Tunón et al., 1995	Weak antiplatelet activity of the Menyanthes leaves water extract lyophilizate in this test
	Water (20°C) two-step extract, (1:20) and (1:10) combined and lyophilized	Antiinflammatory activity. In vitro prostaglandin biosynthesis assay	Tunón et al., 1995	Mild prostaglandin inhibition by activity of the Menyanthes leaves water extract lyophilizate in prostaglandin inhibition

3.1.2. Secondary pharmacodynamics

Menyanthes trifoliata L, folium, extracts

Antimicrobial activities

Extract of the *Menyanthes trifoliata* L., leaves, DER (1:1) obtained with ethanol 55% (v/v), containing secoiridoid bitter agents, dissolved in water, to obtain an extract (1:7) was tested against Gram-positive and Gram-negative bacteria and yeasts showing weak activity (Weckesser et al. 2007

Extract of the leaves from Slovakia (Lieštany) DER 1:200, extraction solvent ethanol 80% (V/V) tested with disc-diffusion method. showing also weak activity against selected Gram-positive and gram negative bacteria (Ivanišova et al. 2017).

Acetylcholinesterase inhibition assay

Dry extracts of 2 g powdered Menyanthes trifoliata L., leaves, with methanol and hexane, were tested on their inhibitory activity against acetylcholinesterase and butyrylcholinesterase. The extracts in concentrations 100 - 400 µg/ml inhibited AChE between 17.1±1.6% – 35.7±2.0% and 22.5±3.6% – 43.8±3.9%. Though the activities were not pronounced (Wszelaki 2010).

Loganin

Antiinflammatory, antioxidative effects on liver and pancreas in diabetic and atherosclerotic models

Yamabe N et al. 2010 studied loganin, orally administered to C57BLKS/J db/db (diabetic II) or non-diabetic as a control, in doses 20 or 100 mg/kg/bw for 8 weeks. Loganin caused slightly decrease of diabetes induced body weight gain, at 100 mg/kg markedly decreased glucose, triglyceride and total cholesterol levels in the liver, decreased by 76-91% expressions of mRNA levels of genes involved in the synthesis of fatty acid and cholesterol in hepatic tissue and attenuated the increase in expressions of hepatic advanced glycation endproduct-related proteins (RAGE, CML, and CEL). Loganin suppressed the nuclear expression of NF-κBp65 in the liver and in a dose of 100 mg/kg reduced COX-2 and iNOS nearly to the level of 'healthy' animals.

Park C-H et al. 2011 administered orally loganin to diabetic II type male mice (C57BLKS/J)db/db or to non-diabetic control; in doses 20 or 100 mg/kg/bw for 8 weeks. In the group administered with loganin the weight and food intake were decreased, loganin at 100 mg/kg/bw significantly decreased elevated values of glucose and leptin and inhibited the levels of hepatic reactive serum oxygen species (ROS). Administration of 100 mg/kg loganin in mice down-regulated oxidative stress-associated biomarkers in hepatic tissues, elevated expression of proteins in hepatic tissues: hepatic Nox-4, p22phox, proteins associated with oxidative stress NF-κBp65, COX-2 and iNOS also Nrf-2, H)-1 protein MCP-1, ICAM as well as Bax, Bcl-2 and cytochrome C protein.

Kim M-J et al. 2015 administered orally loganin to female C57BL/6 mice with caerulein induced acute pancreatitis (AP), in doses 10, 20, 50, 100 mg/kg or control saline. Mice treated with loganin in the doses showed the reduced severity of pancreatitis. The lungs in loganin pre-treated mice had less edema and inflammation compared to the control. Administration of loganin reduced the level of amylase in the pancreas and serum. Loganin significantly inhibited pancreatic mRNA, protein and serum levels of IL-1beta and TNF- increased during acute pancreatitis. In a dose 100 mg/kg in mice loganin inhibited the degradation of 1κ-B alpha, translocation of the p65 nucleus, and NF-κB binding activity. The authors suggested that the effect of loganin on pancreatitis may be associated with the decrease in acinar cell injury and cytokine production due to inhibition of NFκB activation.

Li et al. (2016) studied protective loganin activity against atherosclerotic inflammatory processes on mouse BALB/c model in vivo and in mouse cultured adipocytes 3T3L1 in vitro. The effects of loganin were observed in Tyloxapol-induced mice. Total cholesterol and glucose levels in mice groups administered with loganin (50, 100, 200 mg/kg) and fenofibrate were markedly reduced in compare with Tyloxapol group. The in vitro studies shown, in apoCIII- induced mouse adipocytes significantly reduced the increase of cytokine production: TNF-α, MCP-1, IL-6 and its gene expressions by loganin (32, 64, 128 μM). Pretreatment with loganin inhibited apoCIII-induced activation of NFκB (IκB and p65) activation. The test with Oil Red staining, showed reduced droplets production in mice liver what also suggest the protective activity of loganin (50,100, 200 mg/kg) in inflammatory processes.

Central nervous system effects

Learning and memory impairment experiments. Neuroprotective effects

Kwon et al. (2009) investigated the effect of loganin administered p.o., on learning and memory impairments induced by scopolamine (0.5 mg/kg), in the Y-maze test, passive avoidance, and the Morris water maze. The authors found a significant improvement of memory impairment by loganin, which in doses 20, 40 mg/kg significantly reversed scopolamine-induced impairment, the passive avoidance, and the Morris water maize tests. Also, the next day, loganin dose-dependently increased the latency time in the target quadrant. Moreover, loganin significantly inhibited acetylcholinesterase in the hippocampus and frontal cortex.

Babri et al. 2013 studied the effect of single-dose administration of loganin on spatial memory in diabetic male Wistar rats. The animals were divided into 6 groups: control, diabetic (1 week), diabetic (12 weeks), loganin, diabetic (1 week) + loganin, diabetic (12 weeks) + loganin. Diabetes was induced with

streptozotocin (60mg/kg). Loganin was administered in dose 40mg/kg 1 hour before the test. Spacial memory was compared between groups with Morris water maze. Administration of loganin during acquisition, decreased significantly ($p<0.05$) escape latency and travelling distance to find hidden platform by diabetic rats (both 1 and 12 weeks) and a single dose of loganin improved spatial memory in diabetic rats.

Xu et al. (2017) observed neuroprotective effects of loganin on C57BL/6 mice model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP). The animals were divided into 5 groups administered with: saline, saline + MPTP (first saline and then MPTP), loganin + MPTP (first loganin, then MPTP), MPTP + loganin, loganin + MPTP. Striatal dopamine content was measured to determine whether loganin have a neuroprotective effect in MPTP-induced Parkinson's desease in mice. In a group of loganin + MPTP dopamine level was decreased by 58.1% and in MPTP + loganin by 61.6% ($p<0.001$) wersus saline. Post-treatment with loganin (50 mg/kg) with MPTP increased by 20.3% ($p<0.05$) level of striatal dopamine (DA) versus saline while pre-treatment have no effect. Loganin rescued decrease of tyrosine hydroxylase expression in the striatum corneum (34.2%) and in pole test on bradykinesia shortened this efect (18.5%).

Co-hypnotic effect, effects on sleep

Shi et al. 2019 tested loganin i.v. versus etazolam in mice with subhypnotic dose of pentobarbital. Loganin significantly increased sleep onset: 5 mg/kg 30%, 20 and 50 mg/kg 60% (etazolam 100%). The locomotor activity after injection of loganin, was significantly decreased by the doses 20 and 50 mg/kg. Oral dose of 50 mg/kg loganin increased sleep time compared to vehicle control but has no effect on the decreased sleep time induced by caffeine. In 5 mg/kg, oral dose of loganin nor 5-HTP 2.5 mg/kg i.p., individually affected sleep latency nor pentobarbital subhypnotic sleep time, but coadministration of them shortened sleep latency and prolonged sleep time. Oral dose 35 mg/kg of loganin prolonged total sleeping time on a base EEG and EMG, increased the ratio NREM sleep, shortened wakefulness, increased REM sleep, similarly to etazolam, increased the ratio 5-HIAA/5-HT and decreased the concentration of 5-HT, dopamine and DOPAC in the prefrontal cortex.

3.1.3. Safety pharmacology

No data

3.1.4. Pharmacodynamic interactions

There is no data available on pharmacodynamic interactions.

3.1.5. Conclusions

Primary pharmacodynamic data on bogbean leaf preparations are limited to only two results of tests indicating mild or weak anti-inflammatory activity of water extracts, prepared at room temperature although most of the currently used herbal substances are prepared in a form of infusions.

In the assessment the results of assays for loganin abilities were evaluated. Loganin is one of the main bitter compounds of Menyanthidis trifoliatae folium, exhibiting choleretic and hepatoprotective activity and a trend to normalization of disturbed hepatic and pancreatic functions and also influence blood glucose mostly lowering it after oral administration in mice. Some tests *in vitro* indicated anti-inflammatory activity.

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

Pharmacokinetic data on a bogbean preparations are not available.

Loganin

There are data on loganin, a substance being regarded as an analytical marker of bogbean leaf in the European Pharmacopoeia monograph. However its pharmacokinetic data may be representative for other similar polar iridoid glycosides (mentioned in p. 1.1) they does not reflect the whole pharmacokinetic profile of the preparations.

The absolute bioavailability of loganin was calculated to be 13.2%; only 5% of it was detected in urine, very little in bile and was not detected in feces. (Li et al. 2006, 2008). The authors suggested that loganin may be metabolized in the liver or by intestinal bacteria. In further work on the metabolism by intestinal flora in vivo and in vitro, were found two metabolites. One was loganin aglycone (log-2) which was found to be excreted with bile and eliminated with feces and the second (log-1) was new metabolite which is eliminated with urine (Li et al. 2008).

According to the available publication on tissue distribution of loganin in Sprague-Dawley rats after its oral administration in dose 20 mg/kg (Li et al 2006), the HPLC analyses 15, 45, 90, 180 and 360 min after administration were carried out. 15 min after administration loganin was found in every tested tissues: heart, liver, spleen, kidney, brain, stomach and small intestine. The highest amounts were found in the stomach and small intestine which correlated with a way of administration. In the referred report, peak levels after 90 min were found in most abundant blood-supply tissues such as kidney, lung, liver, and spleen which coincided with the results from plasma. The distribution of loganin was depended on the blood flow or perfusion rate of the organs with the highest AUC of loganin in kidneys (238% of the value in plasma) and lowest in the brain (7% of that in plasma). The kidney was found to be primary excretion organ. There was no long-term accumulation of loganin in tissues. The tested compound was found difficult to cross the blood-brain barrier.

Available pharmacokinetic data on loganin a substance with a specially polar character suggest that its availability from water extracts and powdered herbal substance may be better (with quicker elimination with urine) than from ethanolic extracts and tinctures while less polar secoiridoids (like sweroside) may be better available from intestinal mucosa.

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

No data are available for herbal substance preparations nor for known compounds.

3.3.1. Single dose toxicity

No data available

3.3.2. Repeat dose toxicity

No data available

3.3.3. Genotoxicity

Bogbean leaves which are a green part of the plant contains flavonoids and phenolic acids. Isolated phenolic acids, like chlorogenic, are known to be convertogenic and clastogenic in tests *in vitro*, caffeic

acid, and quinic acids is also genotoxic in vitro. Schimmer et al. 1994 tested commercially available bogbean extracts: Trifolii fibrini extractum siccum[4], from leaves, Trifolii fibrini extractum fluidum, (1:1), extr. solvent ethanol 25% (V/V); Trifolii fibrini tinctura, (1:5) extr. solvent 70% (V/V) and Trifolii fibrini tinctura, (1:5) extr. solvent 60% (V/V) with mutagenic activity Ames test on TA98 and TA100 *Salmonella typhimurium* strains. The dry extract[5] from bogbean leaves was not mutagenic in any test, the ethanolic extract and tinctures gave moderate or weak activity, with increase when S9 mix was added to the test suspension (metabolic activation). The used testing methodology does not fulfill contemporary needs for mutagenicity testing on four *Salmonella typhimurium* strains and with the use methabolic activation. On the base of TLC analyses the authors suggested that the mutagenic component was possibly quercetin. Its presence in Trifolii fibrini tincture and extract corelated with the TLC.

3.3.4. Reproductive and developmental toxicity

No data available

3.3.5. Local tolerance

No data available.

3.3.6. Other special studies

Menyanthes trifoliata L. leaves extract fractions, obtained by the protocol including 50% ethanol extraction for purification of polypeptides, was screened for cytotoxic activity (Lidholm et al. 1998) against 10 human tumor cell lines. The IC_{50} of the extracts was in a range of 33.4 and 132.4 µg/ml. IC_{50} for 6 of 10 strains was below 50 µg/ml, but they were not eminent.

3.3.7. Conclusions

Bogbean leaves do not contain any constituents with safety concerns.

No adverse events were recorded for the herbal substance.

3.4. Overall conclusions on non-clinical data

Non-clinical data on bogbean leaves preparations are scarce but eminent bitter, with influence to the growth of bile secretion by loganin aglycone content supporting the plausibility of the traditional use against lack of appetite and digestion stimulant Results from relevant experimental studies on *Menyanthes trifoliata* L., folium, activity to support the proposed indications are very limited.

Specific data on pharmacokinetics is scarce and data on interactions are not available.

Non-clinical information on the safety of *Menyanthes trifoliata* L., folium, preparations is scarce, there are no data on the toxicity. The available data do not suggest safety concern.

4. Clinical Data

No data available**.** Therefore, only the use as a traditional herbal medicinal product is recommended.

[4] In Germany and Austria was used name Trifolii fibrini extractum siccum, in Poland Extractum Menyanthidis in Sweden Extractum Menyanthis.
[5] In pharmacopoeias was used warm or hot water for extraction.

4.1. Clinical pharmacology

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

No data available

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

No data available

4.2. Clinical efficacy

No data available

4.2.1. Dose response studies

No data available

4.2.2. Clinical studies (case studies and clinical trials)

No published data on medicinal products containing only preparation of bogbean leaf. Results of clinical trials could not be found.

Therefore, only the use as a traditional herbal medicinal product could be proposed.

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

No data available

4.4. Overall conclusions on clinical pharmacology and efficacy

Not applicable because there are no clinical study data available

5. Clinical Safety/Pharmacovigilance

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

Not applicable because of lack of clinical safety data.

5.2. Patient exposure

No detailed information on patients exposure available.

5.3. Adverse events, serious adverse events, and deaths

No data are available from the bibliography.

Searching for data on *Menyanthes trifoliata*, folium, preparations in pharmacovigilance databases revealed no records in European system EUDRA vigilance and no record in the WHO database.

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 clinical data are available.

5.5.2. Contraindications

Searching for data on *Menyanthes trifoliata*, folium, preparations in pharmacovigilance databases revealed no records on adverse events in European system EudraVigilance and no record in the WHO database.

Currently registered in EU products containing bogbean leaf are contraindicated in hypersensitivity to the active substance and in patients with active gastric or duodenal ulcer.

The British Herbal Pharmacopoeia in the monograph Menyanthes contains contra-indications: *In diarrhoea, dysentery or colitis*. This was applicable for dried leaves, liquid extract and tincture mentioned in Table 3.

5.5.3. Special Warnings and precautions for use

According to the Nevall et al. excessive doses may be irritant to the gastro-intestinal tract causing diarrhoea, griping pains, nausea, and vomiting (Nevall et al. 1996 after Martindale The Extra Pharmacopoeia 25th ed. 1967).

The ESCOP monograph (2013) cites the warnings of the BHP: *Not recommended in cases of diarrhea, dysentery or colitis.* In cases of diarrhea and colitis the bitter preparations are not advised but in case of dysentery symptoms (*entoameoebiosis* or *shigellosis*) patient should immediately contact the doctor.

Suggestions on influence of bogbean preparations on gall stones movements can't be confirmed on a base of available medical data.

In consistency with previous herbal monographs with Indication 3, is accepted that: Patients with articular pain accompanied by swelling of joints, redness or fever should be examined by a doctor.

5.5.4. Drug interactions and other forms of interaction

No data available

5.5.5. Fertility, pregnancy and lactation

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

No fertility data are available.

5.5.6. Overdose

No case of overdose has been reported.

Large dose of bogbean are cited to be 'purgative' and may cause vomiting (Nevall *et al.* 1996 after Martindale 1967). However no original data was cited in manuals, the physiological laxative effect of reaction to intense bitter substance is known. No data on the dose nor the case description are available. Due to the possible choleretic effect of iridoid compounds contained in the leaf, a mild laxative effect connected to the bile stimulation by high doses, can't be excluded.

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

No data are available.

For tinctures containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', will be included in the Monograph, in p. 4.4. Special warning and precautions for use.

5.5.8. Safety in other special situations

There are no known safety concerns for the oral use of bogbean leaf in the proposed conditions of use. Currently registered in EU products containing bogbean leaf are contraindicated in patients with active gastric or duodenal ulcer. Therefore, this contraindication has been included in the monograph (4.3).

5.6. Overall conclusions on clinical safety

No data available

6. Overall conclusions (benefit-risk assessment)

The use of *Menyanthes trifoliata* L. preparations has a long tradition in Europe in three kinds of indications:

- in temporary loss of appetite;
- for the relief of mild digestive disorders,
- for relief of minor articular and muscular pain.

As adequate clinical studies have been lacking, the well-established use of the preparations of this herbal substance is not justified.

The medicinal use has been documented continuously in well-known handbooks and authorization regulatory documents.

Herbal teas have been used traditionally in continental Europe in the main indications: temporary loss of appetite and in mild digestive disorders. This kind of indications, as well as traditionally used range of dosages and posologies, are appropriate in adults.

Further it has been agreed the use of bogbean preparations iii)for minor articular and muscular pain. The preparations of *Menyanthidis trifoliatae herba* fulfils the requirements of Directive 2004/24 EC as basis for classification as a traditional herbal medicinal product. The use of bogbean containing preparations in above-mentioned indications is considered plausible on the basis of bibliographic and pharmacological data.

Proposed and used analytical marker in *Menyanthidis trifoliatae folium* in the European Pharmacopoeia monograph (No 1605) is loganin.

Due to the lack of appropriate data on mutagenicity and genotoxicity, carcinogenicity, reproductive and developmental toxicity a list entry for *Menyanthidis trifoliatae herba* cannot be recommended.

There are no clinical safety data for extracts of bogbean leaf preparations. In the documentation of the traditional medicinal use within the Community, no serious adverse effects have been recorded nor confirmed. Search for data on Menyanthes trifoliata (and its synonyms) in EUDRA vigilance system and in WHO pharmacovigilance databases resulted with no reports on adverse events.

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

Annex 1

List of references