EUROPEAN MEDICINES AGENCY
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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Menyanthes trifoliata* L., folium

Final

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)	Menyanthidis trifoliatae folium
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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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 a very bitter and persistent taste (required bitterness value mininimum 3000) and showing a presence of loganin in thin layer chromatography.

Constituents

(after Steinegger & Weibel, 1951; Krebs 1957, 1958; Battersby, 1968; Rułko, 1969; Ciaceri, 1972; Mel'chakova, 1976; Świątek *et al*., 1986; Steinegger & Hänsel, 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 approximately 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, β-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 (Ph. Eur.:1605) for Menyanthidis trifoliatae folium.

1.2. Search and assessment methodology

For the search for data on the medicinal use of bogbean leaf or its preparations were used: pharmacopoeias, medical and pharmaceutical manuals and books (pharmacognosy and medical practice). 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 data with the use of search engines mentioned below was performed online in the area of medical databases which include data from the scientific and medical press. The search included 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 the 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). Additionally, the information on one combined product containing bogbean leaf, was found in its Summary of Product Characteristics, which is available on the webpage 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, HU, NL, DE, SV, LV information was obtained. According to the information only in Poland mono-preparations containing *Menyanthes trifoliata* L., folium, are currently in the pharmaceutical market. Data on officinal formulas are available from CZ and PL. Data on combination products are available from HU and AT. The data on herbal medicinal products which were approved, registered or authorised for marketing are summarised in Table 1.

Table 1: Overview of data on marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form, strength, posology, duration of use**	**Regulatory status**
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) steep for 10-15 min, strain and drink warm infusion 1-3 times daily SD range 1.3-1.6 g DD range 1.3-4.8 g	Authorization 10.05.1993, PL
Menyanthidis folium	Supplementary for stimulation appetite	Herbal tea, infusion/decoction 1 teaspoon (2.0 g) pour with boiling water, boil 5 min under cover, steep for 10 min, strain. Drink a ¾ glass (150 ml, corresponding 1.5 g) of the prepared herbal tea, 2-3 times daily, 30-60 min before meals SD 1.5 g DD 3.0-4.5 g	Registration Certificate 1992.09.21, PL

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.

Five 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 parts, Agrimoniae herba 10 parts, Menyanthidis folium 7 parts, Hyperici herba 7 parts, Glycyrrhizae radix 3 parts, Levistici radix 3 parts, Menthae piperitae aetheroleum 0.1 parts.

Officinal formulas

Menyanthes trifoliata L., folium, has been traditionally used within the EU and in non-EU countries. It has also been used in combination products which were in use as officinal drugs: herbal tea combinations in a form of infusion, combined tinctures or oral liquids.

Frerichs (1938b) in Hagers Handbuch listed pharmacopoeial combination formulas containing bogbean leaf, under a name of Species amarae or Species amaricantes, from pharmacopoeias of Austria, Croatia, Switzerland, Hungary, Netherlands and Denmark. According to the source (1938c) Menyanthidis trifoliatae folium (‘*Folia Trifolii’*) were used in herbal tea combinations and found in Austrian, Croatian, Helvetic, Hungarian, Dutch and in Danish pharmacopoeias.

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

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

Other commonly used officinal drugs were combination tinctures which were used under a name of Tinctura amara. In the Pharmacopoea Bohemoslovenica I (1947), the tincture contained Folium Menyanthidis 20 g per 100 g. In the 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 the 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

Two 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. The first is a liquid extract (1:5) prepared with ethanol-water (of unknown concentration), with a posology in adults: teaspoon (2.5 ml) used 3 times daily. Indication: to help relieve rheumatic pain. The second product is called tincture and contains an 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, herbal tea combinations are used containing Menyanthidis folium, one to reduce rheumatic pain and as a digestive tonic and four other herbal tea combinations with *Menyanthes trifoliata* 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 to increase intestinal secretion in cases of gastritis with hypoacidity and also as cholagogue. It was commonly used in form of infusion/decoction made of one spoon in a glass of boiling water (200 ml), boiled for 5 minutes, steeped for 1-2 hours and used 5-10 minutes before meals, 3 times daily. There was also used a herbal tea combination of Menyanthidis folium with Absinthii herba 15 + 15 g for infusion as a tea and it was used in a dose of 1 spoon, 2-3 times daily, 15-20 minutes 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 a typical bitter agent recorded by many European national pharmacopoeias as officinal (Roeske, 1955). Herba Trifolii aquatici s. fibrini derived from the 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 the leaf was in use and present in the Farmakopea Polska (Pharmacopoeia 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 (Pharmacopoeia Bohemoslovenica, 1947). It was also known for its use in Latvia (Rubine, 1977). In Poland, the comminuted herbal substance had been used as herbal tea and between the 1950s and the 1970s was prepared as a decoction (Gobiec & Konieczny, 1967; Bobowska, 1977), then as a decoction or infusion (Ożarowski, 1976), and the last 30 years as

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

an infusion. Nowadays, the herbal tea infusion, appears the only form still present in the EU member states' pharmaceutical markets (see below Table 1). According to responses received from EU countries, there is no mono-component product registered or authorized on the base of Directive 2004/24/EC, containing sole *Menyanthes trifoliata*, folium preparation. The products which have been present on a market were licensed by the respective countries 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).

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 does somewhat differ to 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 0.3 g (Olechnowicz-Stępień, 1986).

A soft water extract from the leaves have been also used in Poland and Germany. The Extractum Menyanthidis (Pharmacopoea Polonica II 1937c) (DER 1:2) extraction solvent boiling water, after water evaporation, presented a 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*., 2007/2012), have been used in Britain.

Tincture, DER (1:5), extraction solvent 45% ethanol (BHP, 1983; Newall, 1996, Barnes *et al*., 2007/2012), which have been used in Britain.

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

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form, strength, 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	Infusions: 10.0-20.0 g in 200–250 ml of water Posology: 10 ml (one tablespoon) of the	Urzędowy Spis Leków (Official Register of Drugs in

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form, strength, posology, duration of use,** Single doses (SD) and daily doses (DD) counted as herbal substance	**Reference**
	atony, insufficient bile excretion	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 0.8-2.0 g	Poland), 1950, 1963 Informator Terapeutyczny USL (Therapeutic Handbook for Official Register of Drugs), 1955, 1959
	Also, in neurasthenia and neuralgias		As above
Folium Menyanthidis, comminuted herbal substance for herbal tea infusion or decoction	Dyspepsia, hypo-acidosis, 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 min 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

[2] When 20 g of the herbal substance is used for infusion, one half of added water is absorbed by the herbal substance and lost when removed by the straining. Only the remaining 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.

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form, strength, posology, duration of use,** Single doses (SD) and daily doses (DD) counted as herbal substance	**Reference**
Folium Menyanthidis, comminuted herbal substance for herbal tea, infusion	Oral use: for gastritis and ulcers *Assessor's comment: 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 min 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, hypo-acidosis	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 daily 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 g 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 (2x0.4 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 0.5-1.0 g of comminuted herbal substance by the cold water, then heating decocts briefly and after 5-10 min pass through a tea strainer. Drink a cup (150 ml) of the unsweetened infusion or	Wichtl M, 1984

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form, strength, posology, duration of use,** Single doses (SD) and daily doses (DD) counted as herbal substance	**Reference**
		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	
	In minor articular and muscular pain		
Folium Menyanthidis, comminuted herbal substance for herbal tea, infusion	Adults. In minor articular and muscular pain. (See explanations below the Table) Original activity: bitter, diuretic. Indications: rheumatism, rheumatoid arthritis. Specific indications: muscular rheumatism associated with general asthenia	Herbal tea, infusion. 1.0-2.0 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, hypo-acidosis, 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	Ożarowski, 1976

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

Herbal preparation	**Documented use / Traditional use**	**Pharmaceutical form, strength, posology, duration of use,** Single doses (SD) and daily doses (DD) counted as herbal substance	**Reference**
		DD 1.0-2.0 g	
Powdered herbal substance	Lack of appetite in children *Assessor's comment: Age accepted by HMPC 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; 2008
		Adolescents, Adults: SD range 0.3-0.5 g DD range 1.0-2.0 g	
	In minor articular and muscular pain		
Dried leaves, comminuted/powdered	Adults. In minor articular and muscular pain Original activity: bitter, diuretic. Indications: rheumatism, rheumatoid arthritis. Specific indications: muscular rheumatism associated with general asthenia	Dried powdered leaves (capsules) taken in a dose of 1.0-2.0 g thrice daily SD 1.0-2.0 g DD 3.0-6.0 g	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 Original activity: bitter, diuretic. Indications: rheumatism, rheumatoid arthritis. Specific indications:	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

Herbal preparation	Documented use / Traditional use	Pharmaceutical form, strength, posology, duration of use, Single doses (SD) and daily doses (DD) counted as herbal substance	Reference
	muscular rheumatism associated with general asthenia		
Tincture (1:5), extraction solvent 45% ethanol (V/V)	Adults. In minor articular and muscular pain Adults. In minor articular and muscular pain Original activity: 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, the estimated average medium contents of Menyanthidis trifoliatae folium, comminuted herbal substance in this table are: 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 (*Rapporteurs calculations*).

In the first half of the 20th century, bogbean leaf was used in form of strong bitter tea infusions, prepared once for a day and taken in relatively small single doses of 10 ml (1 spoon). For this way of use, the infusion was prepared from 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 a daily use of 2-4 single doses, only 20-40 ml were taken from the total volume prepared for a day (Informator Terapeutyczny USL, 1955, 1959). Although the volume of the preparation was small, its concentration and bitter value was high. This way of tea preparation, for its use during a day in divided doses was common, although in the seventies the single doses had partially a bigger volume of 20-60 ml (Ożarowski 1976, 1978; Rubine, 1977). In Poland, infusions/decoctions have been traditionally prepared using 200-250 ml water (corresponding to '1 glass').

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 Article 3, paragraph 1 and 2 of Directive 2001/83/EC.

Herbal teas have been traditionally used 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 the HMPC to limit the use of the products to adults only, in line with other EU herbal monographs on bitter substances.

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

The traditional use of liquid extracts (DER 1:1) with the extraction solvent ethanol 25% (V/V) in minor articular and muscular pains is also documented by the below-tabled bibliography.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**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 (hypo-acidosis) and digestive function of the stomach (dyspepsia)	Infusion/decoction of 2.2-4.0 g herbal substance in 200 ml [corresponding to 1.6-3.0 g/150 ml] used in single doses 40-50 ml, taken 4-5 times daily, 30 min before meals SD 0.4-0.6 g DD 1.6-3.0 g	Ożarowski 1976; Ożarowski *et al*., 1978
Menyanthidis folium, herbal tea, infusion	Adolescents, Adults 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 times daily Strength: 1.3-1.6 g/150 ml SD range 1.3-1.6 g DD range 1.3-4.8 g	Authorization 10.05.1993, PL
Menyanthidis folium, herbal tea, infusion	Adolescents, Adults	Herbal tea, infusion. 1 teaspoon declared to be 2.0 g pour with boiling water, boil for 5 min under cover, steep for 10 min, strain.	Registration Certificate 1992.09.21, PL

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Supplementary for stimulation of appetite	Drink ¾ glass (150 ml, corresponding 1.5 g) of the prepared decoction, 2-3 times daily, 30-60 min before meals Strength: 1.5 g/150 ml SD 1.5 g DD range 3.0-4.5 g	
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 0.5-1.0 g of comminuted herbal substance, used in both indications, 3 times daily, 30 min 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 1.0-2.0 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. 1.0-2.0 g for one cup of infusion (150 ml). Used thrice daily Duration of use not restricted	British Herbal Pharmacopoeia, 1983

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		Strength: 1.0-2.0 g/150 ml SD range 1.0-2.0 g DD range 3.0-6.0 g	
Tincture, DER (1:5), extraction solvent 45% ethanol (V/V)	Adults In minor articular and muscular pain	SD 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 SD 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 preparation fulfils the criteria of traditional medicinal use throughout at least 30 years including 15 years of tradition within the European Union 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

a. 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 minutes before meals, in Indication 2) between meals.

Daily doses: 0.8 g - maximum 4.8 g.

Indication 1)

b. 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 minutes before meals.

Daily doses: 1.5 g to 4.5 g.

Adults

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

Daily dose 1.5-2.0 g.

Indication 3)

Adults and Elderly

a) Herbal tea: 1.0-2.0 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 1.0-2.0 g, 3 times daily

c) Liquid extract (DER 1:1) extraction solvent ethanol 25% (V/V). Single dose 1-2 ml, 3 times daily

d) Tincture (DER 1:5), extraction solvent 45% ethanol (V/V). Single dose 1-3 ml, 3 times daily

3. Non-Clinical Data

Non-clinical data on bogbean leaf or its extracts is 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 obtained with traditionally used preparations and connected with its use in traditional indications.

Digestive stimulation

Supportive for the activity of *Menyanthes trifoliata* preparations are available data for loganin, the bitter compound of the leaves. Reported are stimulation of digestive functions (Takeda *et al*., 1980) as well as some protective effects on liver and pancreas (Kim *et al*., 2015; Park *et al*., 2011; Yamabe *et al*., 2010).

Anti-inflammatory 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	**Posology, strength, dosage, route of administration**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Loganin, Loganin aglycone	Loganin and loganin aglycone solutions administered iv,	*In vivo*. Anesthetised male Wistar rats (200-250 g);	Takeda *et al*., 1980	Important growth of bile secretion by

Herbal preparation tested	Posology, strength, dosage, route of administration	Experimental model	Reference	Main non-clinical conclusions
	in doses 25 mg/kg and 50 mg/kg	administered *i.v.* with single doses of the tested substances. Bile volume collected at 30 min intervals via common bile duct canulas		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	Anti-inflammatory 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

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

Another extract of bogbean leaves from Slovakia (Lieštany), DER 1:200, extraction solvent ethanol 80% (V/V), was tested using the disc-diffusion method. It showed also a 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

Anti-inflammatory, antioxidant 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 mice as a control, in doses of 20 or 100 mg/kg/bw for 8 weeks. Loganin caused a slight decrease of diabetes-induced body weight gain. At 100 mg/kg it markedly decreased glucose, triglyceride and total cholesterol levels in the liver. It also decreased by 76-91% expressions of mRNA levels of genes involved in the synthesis of fatty acid and cholesterol in hepatic tissue and it attenuated the increase in expressions of hepatic advanced glycation end product-related proteins (RAGE, CML, and CEL). Loganin suppressed the nuclear expression of NF-κBp65 in the liver. At a dose of 100 mg/kg it 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 the non-diabetic control; in doses of 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 of 10, 20, 50, 100 mg/kg or control saline. Mice treated with loganin showed 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-α increased during acute pancreatitis. at a dose of 100 mg/kg in mice loganin inhibited the degradation of 1κ-B α, 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 NF-κB activation.

Li *et al*. (2016) studied the protective loganin activity against atherosclerotic inflammatory processes using the mouse BALB/c model *in vivo* and 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 comparison with the tyloxapol group. The *in vitro* studies showed in apoCIII- induced mouse adipocytes a significantly reduced increase of cytokine production by loganin (32, 64, 128 μM): namely TNF-α, MCP-1, IL-6 and its gene expressions. Pre-treatment with loganin inhibited the apoCIII-induced activation of NF-κB (Iκ-B and p65). The test with Oil Red staining, showed reduced droplets production in mice liver, what, according to the authors, also suggests 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 a 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. The striatal dopamine content was measured to determine whether loganin has a neuroprotective effect in MPTP-induced Parkinson's disease in mice. In the group of loganin + MPTP, the dopamine level was decreased by 58.1% and in MPTP + loganin by 61.6% ($p<0.001$) versus saline, respectively. Post-treatment with loganin (50 mg/kg) with MPTP increased the level of striatal dopamine (DA) by 20.3% ($p<0.05$) versus saline while pre-treatment had no effect. Loganin rescued the decrease of tyrosine hydroxylase expression in the striatum corneum (34.2%) and in the pole test shortened the effect on bradykinesia (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 the 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 had no effect on the decreased sleep time induced by caffeine. Loganin at an oral dose of 5 mg/kg or 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. The oral dose of 35 mg/kg loganin prolonged total sleeping time on a base of electroencephalography (EEG) and electromyography (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 available.

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 some data available on loganin, a substance being regarded as an analytical marker of bogbean leaf in the European Pharmacopoeia monograph. Although, its pharmacokinetic data may be relevant also for other comparable polar iridoid glycosides (mentioned in p. 1.1) they do not reflect the whole pharmacokinetic profile of bogbean 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 it 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 affected by the intestinal flora *in vivo* and *in vitro*, two metabolites were found. One was the loganin aglycone (log-2) which was found to be excreted with bile and eliminated with feces and the second (log-1) was a new metabolite which is eliminated with the urine (Li *et al*., 2008).

Li *et al. (*2006) studied the tissue distribution of loganin in Sprague-Dawley rats after its oral administration (20 mg/kg). HPLC analysis was carried out at 15, 45, 90, 180 and 360 minutes after administration. 15 minutes after administration loganin was found in every tested tissue: heart, liver, spleen, kidney, brain, stomach and small intestine. The highest amounts were found in the stomach and small intestine which correlated with the way of administration. Peak levels after 90 minutes 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 to hardly 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 the 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 contain 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 are 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), extraction solvent ethanol 25% (V/V); Trifolii fibrini tinctura, (1:5) extraction solvent 70% (V/V) and Trifolii fibrini tinctura, (1:5) extraction solvent 60% (V/V) for mutagenic activity using the 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, which increased when the S9 mix was added to the test suspension (metabolic activation). The used testing methodology does not fulfil contemporary needs for mutagenicity testing on four *Salmonella typhimurium* strains with the use of metabolic activation throughout. 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. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

Menyanthes trifoliata L. leaves extract fractions, obtained by the protocol including 50% ethanol extraction for purification of polypeptides, were screened for cytotoxic activity against 10 human tumour cell lines (Lindholm *et al*., 2002). The IC_{50} of the extracts was in a range of 33.4-132.4 µg/ml IC_{50} for 6 of 10 strains was below 50 µg/ml, but they were not eminent.

3.3.8. Conclusions

Bogbean leaves do not contain any constituents with known 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. Nonetheless. as an eminent bitter, with influence to increase bile secretion, the loganin (aglycone) content supports the plausibility of the traditional use against lack of appetite and as a digestion stimulant. Regarding activity, results from relevant experimental studies on *Menyanthes trifoliata* L., folium, are very limited to support the proposed indications.

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

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

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

4. Clinical Data

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

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 patient's exposure available.

5.3. Adverse events, serious adverse events, and deaths

No data is available from the bibliography.

Searching for data on *Menyanthes trifoliata* L., folium, preparations in pharmacovigilance databases revealed no records in the EudraVigilance database 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 is available.

5.5.2. Contraindications

Menyanthes trifoliata L., folium, preparations have currently no records on adverse events in pharmacovigilance databases (EudraVigilance and WHO database).

Currently registered 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 monograph *Menyanthes* gives following contra-indications: in diarrhoea, dysentery or colitis. This was applicable for dried leaves, liquid extract and tincture listed in Table 3, section 2.3. of this report.

5.5.3. Special Warnings and precautions for use

According to Newall *et al*. excessive doses may be irritant to the gastro-intestinal tract causing diarrhoea, griping pains, nausea, and vomiting (Newall *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 diarrhoea, dysentery or colitis. In cases of diarrhoea and colitis the bitter preparations are not advised but in case of dysentery symptoms (entoameoebiosis or shigellosis) patients should immediately contact a doctor.

Suggestions on the 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) (Minor articular and muscular pain), 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.

Taking a large dose of bogbean is reported to be 'purgative' and may cause vomiting (Newall *et al*., 1996 quoting Martindale, 1967). However, no original data was cited in any manuals. A laxative effect as a physiological reaction to intense bitter substance is known. Neither data on the dose nor on the case description is available. Due to the possible choleretic effect of iridoid compounds contained in the leaf, a mild laxative effect connected to the bile stimulation caused 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 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 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 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. These kinds of indications, as well as the traditionally used range of dosages and posologies, are appropriate in adults.

Further it has been agreed the use of bogbean preparations for minor articular and muscular pain. The preparation of Menyanthidis trifoliatae herba fulfills 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.

The proposed analytical marker in Menyanthidis trifoliatae folium is the one already used in the European Pharmacopoeia monograph (No 1605): 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 is no clinical safety data for extracts of bogbean leaf preparations. In the documentation of the traditional medicinal use within the European Union, no confirmed serious adverse effects have been reported. The search for data on *Menyanthes trifoliata* (and its synonyms) in the EudraVigilance system and in WHO pharmacovigilance databases resulted in 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