EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Malva sylvestris* L. and/or *Malva neglecta* Wallr., folium and *Malva sylvestris* L., flos

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)	*Malva sylvestris* L., flos *Malva sylvestris* L. and/or *Malva neglecta* Wallr., folium
Herbal preparation(s)	*Malva sylvestris* L., flos Comminuted herbal substance *Malva sylvestris* L. and/or *Malva neglecta* Wallr., folium Comminuted herbal substance
Pharmaceutical form(s)	*Malva sylvestris* L., flos Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for infusion or decoction preparation for oromucosal use. *Malva sylvestris* L. and/or *Malva neglecta* Wallr., folium Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for infusion or decoction preparation for oromucosal use
Rapporteur	Ewa Widy-Tyszkiewicz
Peer-reviewer	Marie Heroutova

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 x
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

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

- Herbal substance(s)

***Malva sylvestris* L., flos**

Mallow flower (Malvae sylvestris flos) consists of the whole or fragmented dried flower of *Malva sylvestris* L. or its cultivated varieties. The flower consists of an epicalyx with 3 oblong or elliptical-lanceolate parts that are shorter than those of the calyx and situated immediately below it; a calyx with 5 pubescent triangular lobes, gamosepalous at the base; a corolla 3-4 times longer than the calyx with 5 wedge-shaped, notched petals fused to the staminal tube at their base; numerous stamens, the filaments of which fuse into a staminal tube covered by small star-shaped trichomes and occasional simple trichomes visible using a lens; numerous wrinkled carpels, glabrous or sometimes pubescent, enclosed in the staminal tube and arranged into a circle around a central style ending with numerous filiform stigmas. In cultivated varieties, the epicalyx is 3-7 partite, the calyx 5-8 partite and the corolla 5-10 partite (European Pharmacopoeia 9th edition, 1541).

***Malva sylvestris* L., *Malva neglecta* Wallr. or a mixture of both species, folium**

Mallow leaf (Malvae folium) represents whole or fragmented, dried leaf of *Malva sylvestris* L., *Malva neglecta* Wallr. or a mixture of both species. The leaves of *M. sylvestris* are up to 12 cm long and up to 15 cm wide with 3, 5 or 7 lobes and sinuate at the base; the leaves of *M. neglecta* are up to 9 cm long and wide, round or kidney-shaped with 5-7 indistinct lobes. The leaves of both species have irregular dentate margins and are green or brownish-green. The abaxial surface of the lamina bears more hairs and shows a more prominent venation than the adaxial surface. The major veins on the upper surface of the leaves and the petioles may be violet. The petioles are as long as the leaves, up to 2 mm wide, rounded and somewhat flattened, longitudinally slightly grooved, green or brownish-green or violet. The fragmented drug consists of occasionally agglomerated, crumpled pieces of leaves showing prominent veins (European Pharmacopoeia 9th edition, 2391).

- Herbal preparation(s)

Malvae sylvestris flos

Comminuted herbal substance as herbal tea for oral use or for infusion or decoction preparation for oromucosal use.

Malvae, folium

Comminuted herbal substance as herbal tea for oral use or for infusion or decoction preparation for oromucosal use.

The following compounds were found in *Malvae sylvestris* flowers:

- Mucilage polysaccharides

The basic structural unit of polysaccharides consisting of glucose, galactose and rhamnose occurs in different proportions in both flowers and leaves of *Malva sylvestris*. It appears that high molecular weight acid polysaccharides are responsible for the viscosity and increase of the swelling index in aqueous solutions. About 10% of mucilage is present in flowers.

Classen and Blaschek (1998) in: Flores (2011), Čapek (1992), Čapek and Kardošova (1995) and Čapek *et al.* (1999) isolated four polysaccharides from the flowers of *Malva sylvestris* L. sp.: a linear neutral polysaccharide, a branched neutral polysaccharide, high molecular weight acid polysaccharides and a very branched acidic polysaccharide. The molecular weight of the high molecular weight acidic polysaccharide was in the range of 1.6×10^6 Da. It consisted mainly of glucuronic acid, galacturonic acid, rhamnose and galactose. The amount of uronic acids, galacturonic and glucuronic, in *Malva sylvestris* is much higher in flowers (22.8%) than in leaves (8.2%).

Čapek *et al.* (1999) isolated from *Malva sylvestris* sp. *mauritiana* a neutral heteropolysaccharide with relative molecular weight 3.71×10^6. It consisted of the dominant compound L-rhamnose (42%) followed by L-arabinose (34.3%), D-galactose (23.4%) and traces of D-mannose, D-xylose and L-fucose. The investigations indicated a branched structure of the polysaccharide with 3.6-linked D-galactopyranose, 5-linked L-arabinofuranose as well as 4-linked and terminal L-rhamnopyranose residues as the main building units.

Hydrolysis of the mucus polysaccharides results in the release of neutral sugars: glucose, arabinose, xylose and rhamnose (Hänsel *et al.* 1994, Wichtl 1994).

- Anthocyanins

Malvidin 3, 5-diglucoside, malvidin 3-glucoside, malvidin 3-(6-malonylglucoside)-5-glucoside, delphinidin 3-glucoside, petunidin, cyanidin, malvidin chloride were identified; total anthocyanin content ranged from 0.42 to 7.3% of dry matter (Farina *et al*. 1995; Takeda *et al*. 1989; Alesiani *et al*. 2007, Vadivel *et al*. 2016).

- Other constituents

Other flavonoids

The following flavonoids were found in Malvae flos: luteolin, kaempferol, myricetin, apigenin, genistein quercetin (Loizzo *et al*. 2016, Alesiani *et al*. 2007, Pourrat *et al*. 1990; Farina *et al.* 1995; Takeda *et al*. 1989). Kaempferol-3-O-rutinoside and quercetin-3-O-rutinoside were the main flavonols in M. sylvestris identified by Barros *et al*. (2012). Additionally, caffeoylquinic acid, quercetin acetyldihexoside, luteolin-, apigenin- and chrysin- derivatives as well as kaempferol hexoside and kaempferol acetylhexoside were found by Barros *et al*. (2012) in Malvae sylvestris flos.

Fatty acids

The following fatty acids were found: palmitic acid, pelargonic acid, stearic acid, α-linolenic acid (Loizzo *et al*. 2016).

Other organic acids

Other organic acids found by Pereira *et al*. (2013) are oxalic acid; malic acid; ascorbic acid; citric acid; fumaric acid

Essential oil-0.039% (w/w) of essential oil containing 143 volatile compounds was obtained from dried flowers. The essential oil consisted mainly of hydrocarbons (25.40%) followed by, alcohols (18.78%), acids (16.66%), ethers (5.01%) ketones (7.28%), esters (12.43%), aldehydes (2.30%) and others (2.30%). The main components found were hexadecanoic acid, 2-methoxy-4-vinylphenol and pentacosane. β-Damascenone, phenylacetaldehyde and (*E*)-β ocimene were the most intense aroma-active compounds (Usami *et al*. 2013).

Carotenoids (Loizzo *et al*. 2016, Alesiani *et al*.2007, Redžić *et al*. 2005).

Chlorophyl A and B (Redžić *et al*. 2005).

Tocopherols (Barros *et al*. 2010).

The following substances were found in *Malvae sylvestris* leaves:

- Mucilage polysaccharides

Malva leaves contain about 6 to 8% of mucilage according to Wichtl (2004) and Gruenwald *et al*. (2000). High molecular weight acidic polysaccharides located in epidermal cells of the leaves were found to be of the rhamnogalacturonan type. The weight of the high molecular weight acid polysaccharides of leaves of *Malva sylvestris* is 1.38 x 10^6 Da with the same basic structural unit consisting of glucose, galactose and rhamnose as in flowers (Classen and Blaschek 1998, in Flores 2011).

A mucilage was isolated from the fresh leaves of *Malva sylvestris* Mill. var*. mauritiana* in which main constituent is acidic polysaccharide with molecular weight about 6.0x10^6. Quantitative analyses showed that this polysaccharide was composed of 94.4% polysaccharide and 5% peptide moieties. The polysaccharide contained 40% L-rhamnose, 22.2% D-galactose, 16% D-galacturonic acid and 16% D-glucuronic acid in the molar ratio 6:3:2:2 (Tomoda *et al*., 1989). Samavati and Manoochehrizade (2013) isolated crude polysaccharides from the leaves of *Malva sylvestris*. The experimental yield of polysaccharides was 8.38±0.38%. Gonda *et al*. (1990) isolated from the leaves of *Malva sylvestris*. L, var. *mauritiana* Mill. an acidic polysaccharide with molecular weight of 11000 Da, composed of L-rhamnose, D-galactose, D-galacturonic acid, and D-glucuronic acid in the molar ratio of 22:6:22:11 and containing 7.7% peptide.

- Other constituents

Phenolic derivatives

The total phenolic compounds were found to be 386.5 mg/g in the leaves (Barros *et al*. 2010).

Polyphenols

Presence of the following polyphenols is reported in the literature sources: 4-hydroxybenzoic acid, 4 methoxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid, 2-hydroxybenzoic acid, 4-hydroxy-2 methoxybenzoic acid, 4-hydroxybenzyl alcohol, 4-hydroxydihydrocinnamic acid, 4-hydroxy-3 methoxydihydrocinnamic acid, 4-hydroxycinnamic acid, ferulic acid and tyrosol (Cutillo *et al*. 2006), chlorogenic acid (in herb) (Terninko *et al*. 2014).

Flavonoids

The presence of gossypetin 3-sulphate-8-*O*-β-D-glucoside (gossypin) and hypolaetin 3-sulphate as the major constituents, followed by hypolaetin 4-methyl ether 8-*O*-D-glucuronopyranoside, hypolaetin 8 *O*-β -D-glucuronopyranoside and isoscutellarein 8-*O*-β-D-glucuronopyranoside was found (Billeter *et al*. 1991, Nawwar *et al*. 1977, Nawwar and Buddrus 1981). Luteolin, rutin, epicatechin were found by

Terninko *et a*l. 2014. Quercetin, kampferol and myricetin were identified by Alesiani *et al*. 2007 in herb of *Malva sylvestris.*

Terpenoids

linalool-1-oic acid, (6R,7E, 9S)-9-hydroxy-4,7-megastigmadien-3-one, (3S,5R,6S,7E, 9R)-5,6-epoxy 3,9-dihydroxy-7-megastigmene, blumenol A, (3R,7E)-3-hydroxy-5,7-megastigmadien-9-one, (+)-dehydrovomifoliol, (3S,5R,6R,7E,9R)-3,5,6,9-tetrahydroxy-7-megastigmene and (6E,8S,10E,14R) 3,7,11,15-tetramethylhexadeca-1,6,10-trien-3,8,14,15-tetraol. (Cutillo *et al*. 2006)

(3R,7E)-3-hydroxy-5,7-megastigmadien-9-one (DellaGreca *et al*. 2009).

Carotenoids

(Barros *et al*. 2010, Terninko *et al*. 2014, Terninko and Onishchenko, 2013).

Coumarins

Coumarin was identified by Terninko *et al*. (2014), 5,7-dimethoxycoumarin by Alesiani *et al.* (2007) and 7-hydroxy-6-methoxycoumarin (scopoletin) by Tosi *et al.* (1995) and DellaGreca *et al*. (2009)

Organic acids

Presence of ascorbic acid, dehydroascorbic acid, oxalic acid is refered by Guil *et al.* (1997); citric acid, oxalic acid and malic acid by Terninko *et al*. (2014) and Terninko and Onishchenko (2013) and (10E,15Z)-9,12,13-trihydroxyoctadeca-10,15-dienoic acid by DellaGreca *et al.* (2009).

Major and minor elements - Ag, Al, B, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, La, Mg, Mn, Na, Ni, Pb, Sn, Sr, Sb, Si, Ti, U, Zn, Zr (Hiçsönmez *et al*. 2009).

Bis (2-ethylhexyl) phthalate (Zakhireh *et al*. 2013), *Malvone A (2-methyl-3- methoxy-5,6-dihydroxy-1,4-naphthoquinone)* (Veshkurova *et al*. 2006), *Trigonelline and glycine betaine* (Blunden *et al*. 2001).

Methyl 2-hydroxydihydrocinnamate, N-trans-feruloyl tyramine (DellaGreca *et al.* 2009), *Nitrates* (Terninko *et al.* 2014, Terninko and Onishchenko 2013).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

1.2. Search and assessment methodology

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on *Malva sylvestris* L.

Databases assessed up to October 2017: Science Direct, PubMed, Embase, Medline, Academic Search Complete, Toxnet

Search terms: Malva sylvestris, Malva neglecta, common mallow

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

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following herbal substances/preparations have been marketed in the EU/EEA:

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Malva sylvestris L., flos	Traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough.	Herbal tea Oral use: 1.0 g of the comminuted herbal substance in 250 ml of boiling water as a herbal decoction. Drink 2-3 times daily corresponding to the maximum daily dose of 3 g.	Poland Used for more than 30 years Date of TU registration: 10/07/2010 Registration as traditional herbal medicinal product according to Directive 2004/24
Malva sylvestris L., folium	Irritation of the mucous membrane in the mouth and throat and associated dry cough	Herbal tea: >12 years Oral use: 1.8 g/150 ml boiling water 3 times daily	Germany 1986, DE, Standard Marketing Authorisation According to section 36 of the German Medicinal Products Act
Malvae folium (comminuted herbal substance)	Traditional herbal medicinal product for the relief of: 1. irritations of the mucosa in the mouth and throat 2. irritations of the mucosa in the gastrointestinal tract 3. dry cough 4. supportive treatment of small	1 tea bag contains 1.4 g herbal tea (infusion) 1 tea bag per cup; Adults, adolescents, children >6 years: 3-4 times daily Children 2-5 years (indications 2, 3, 4): 1-2 times daily Duration of use: 7 days	Austria THMP since 2011

Active substance	Indication	Pharmaceutical form	Regulatory Status
	superficial wounds		
Malvae folium (comminuted herbal substance)	Traditional herbal medicinal product for the relief of: 1. irritations of the mucosa in the mouth and throat 2. irritations of the mucosa in the gastrointestinal tract 3. dry cough	1 tea bag contains 1.5 g Herbal tea (infusion) 1 tea bag per cup; Adults, adolescents, children >6 years: 3-4 times daily Children 2-5 years(indications 2, 3): 1-2 times daily Duration of use: 7 days	Austria THMP since 2013

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

None

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

Single active ingredient: 131 herbal teas (Germany).

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

Not applicable

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

There is an evidence of the use of *Malva sylvestris* for the past thousand years in Europe (Gasparetto *et al*. 2012; Prudente *et al*. 2013; Ghédira and Goetz 2016). *Malva sylvestris* remains, together with remains of other medicinal plants, have been found through archaeological research among the oldest Central European inhabitants- living in Lower Saxony more than 6000 years ago (Dieck 1985).

Another species distributed in the same regions is *Malva neglecta* (neglected mallow) which is also used as a source of leaves for medical purposes. In ancient times, the plant was used by the Greeks and Romans for its emollient and laxatives properties.

In current medical practice *M. sylvestris* is used in a variety of inflammatory conditions. In the Mediterranean area, young leaves and stems are eaten in soups and salads either as raw or as cooked vegetables. Besides use in inflammation of the mouth and throat when is applied in a form of infusions, decoctions as a herbal tea or a gargle, cutaneous use for treatment of cuts, infected wounds and skin burns in a form of poultices and lotions is described in literature (Barros *et al*. 2010).

The medicinal use of *Malva sylvestris* leaves and flowers has been documented continuously in several pharmacopoeias: the first information about mallow flowers in Poland is included in Materia Pharmaceutica of the 1st Polish Pharmacopoeia: Pharmacopoeia Regni Poloniae, Varsoviae (1817)where

"Flores Malvae sylvestris; vulgaris" are presented as "flores mucilaginei". Also, in the pharmaceutical lexicon published at the turn of the 19th and 20th century flowers of *Malva sylvestris* are listed (Wiorogórski and Zajączkowski 1892–1918). In classical book by Schimpfky (1900) "wilde Malve-*Malva sylvestris*" is described. Deutsches Arzneibuch DAB 6. Ausgabe(1947) presents common mallow flowers and leaves. Malvae folium and flos was in the in the Czechoslovak Pharmacopoeia first edition 1947, in Austrian Pharmacopoeia (Österreichisches Arzneibuch) 1960, in Pharmacopoea Hungarica 1986, and in Pharmacopoea Helvetica 1997. Pharmacopoea Polonica III (1954) included Malvae Flos. European Pharmacopoeia 9.0th presents both mallow flower (1541) and mallow leaf (2391).

Mallow is traditionally used due to high mucilage content for treatment of the symptoms of oral or pharyngeal irritations, associated dry cough and gastrointestinal discomfort.

In current folk medical practice in Italy *Malva sylvestris* use is widely used, where a large number of ethnobotanical information from comes. Decoctions of the leaves are used locally in inflammation of the mouth in the region of the northern Italian Ligurian Alps (Cornara *et al*. 2014). In Valvestino, near Lake Garda also the frequent use of *Malva neglecta* was notified (Vitalini *et al*. 2009). In Lombardy, widespread use both *Malva sylvestris* and *Malva neglecta* Wallr. was recorded as antiflammatory, laxative, emollient decoction on wounds and sores (Vitalini *et al*. 2015). In central Italy, decoctions of aerial parts are used as a laxative and topically applied to the cheek or directly into aching teeth (Guarrera *et al*. 2005). In the central Appenine area *Malva sylvestris* leaves, flowers and whole aerial parts are used in bronchitis, sore throat and cough. Aerial parts are applied to aching teeth as analgesic and as a mouthwash (Idolo *et al*. 2010). In Abruzzo, the plant leaves and flowers are used as emollient, expectorant, diuretic and mild laxative for children (Leporatti and Corradi 2001). In Campania, both aerial parts and leaves are used in throat inflammation, bronchitis and cough (Di Novella *et al*. 2013; Menale and Muoio 2014; Menale *et al*., 2016).

In southern Italy in Basilicata Region decoctions of aerial flowering parts are used as a mild laxative, against flu, cold and stomach ache (Montesano *et al*. 2012; Quave *et al*. 2008 a). In the south of Italy, in the region of Calabria, mallow leaves and flowers in infusions and decoctions are used both locally and systemically in mouth inflammation, toothache as mouthwashes, gargles and as a laxative (Leporatti and Impieri 2007; Passalacqua *et al*. 2007). Also, in Sicily and in Sardinia *Malva sylvestris* flowers and leaves are used in folk traditional medicine as herbal tea for digestive and anti-inflammatory therapy and in gingivitis and toothache (Leto *et al*. 2013; Leonti *et al*. 2009; Tuttolomondo *et al*. 2014; Signorini *et al*. 2009).

In Spain *Malva sylvestris* flowers, leaves and whole aerial parts are applied directly topically, often without pharmaceutical forms as poultice or to prepare bath as antipruritic and external antiseptic treatment (Rigat *et al*. 2015). The plant is used to cure wounds and inflammations and is used as an analgesic, but also as a herbal tea for respiratory problems and stomach ache (Calvo *et al*. 2011, Calvo and Cavero, 2015; González *et al*. 2010). In Portugal, both *Malva sylvestris* and *Malva neglecta* flowers and leaves are used as herbal tea systemically and topically as an anti-inflammatory, antiseptic and antiodontalgic treatment (Novais *et al*. 2004).

In Bosnia-Hercegovina *Malva sylvestris* herbal tea of leaves and flowers is used orally in common cold, dry cough and croakiness, cough, pulmonary ailments, gastrointestinal spasms and painful urination (Sarić-Kundalić *et al*. 2010).

In Serbia, mallow leaves and flowers are topically applied as poultices on wounds and ulcers difficult to heal (Jarić *et al*. 2015).

Table 2: Overview of historical data. The traditional use and indications for *Malva sylvestris* L. flowers in the following handbooks:

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Malvae flos	Traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough and in dyspeptic symptoms	Infusion or decoction prepared from 10–15 g/1 L water Drink 2–4 glasses daily	Muszyński *et al.* 1958
Malvae flos	Oral use as demulcent in throat irritation	As decoction: 0.75 g of flowers on 1 glass of water Drink divided 2–3 times daily	Gobiec and Konieczny, 1967
Flores Malvae sylvestris	Oral use as mucilaginous, in inflammation of upper respiratory tract and throat and in gastroenteritis as mild astringents External use in treatment of wounds	For posology it is referred to ÖAB 9: 1.5 g per cup as infusion or decoction Hung. VI: Single dose 0.5 to 1 g, daily dose 5 g DAB 7: For mouthwash 1.5% infusion	Kern *et al*. 1976
Flores Malvae sylvestris	Oral use used for cough, cold as well as constipation and intestinal inflammation. Topical use: inflammation of the mouth and throat mucous membranes, sensitive gums, toothache, skin redness, furuncles, itching.	Oral use: herbal tea: 3 g per 100 ml of water. 2-3-cups daily	Wurzer (editor) 1994
Malvae flos	Traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough.	Herbal tea: pour 1½ glass (300 ml) of boiling water over 1 table spoon crushed mallow flowers; drink 3 cups daily.	Ożarowski *et al*. 1978
Flores Malvae sylvestris Flowers	Protectivum, demulcens Oral use: traditional herbal medicinal product	Herbal tea: pour 1–1 ½ glass of boiling water over 1–2 table spoons of flowers.	Ożarowski 1982

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
	used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough. Used in laryngitis, pharyngitis	Drink 1/3 of the glass 3 times daily. Used also for gargling in throat irritation. In infants used as an enema.	
Malvae flos	Herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough.	Oral use: 1.5–2 g (1 teaspoon=0.5 g) of is added to cold water and boiled and strained after 10 minutes. Daily dose: 5g	Hänsel *et al*. 1994
Malvae flos	Oral use: as demulcent in irritations of the mucous membrane of the mouth and throat, and the associated dry cough In folk medicine, externally in a form of poultices for treatment of wounds and for baths	Herbal tea: 1.5–2 g of comminuted drug is placed in of cold water, and boiled for a short time, or boiling water is poured over it, and after 10 min. strained. Daily dose: 5 g of drug; preparations correspondingly (taken from Commission E monograph)	Wichtl, 1984; 1994
Flores Malvae sylvestris	Coughs and bronchitis, gastroenteritis	Herbal tea: 2 teaspoons in 250 ml of cold water, left for 30 min; drink 1–3 cups daily after heating or use for gargling	Podlech 1997
Dried Malvae sylvestris flower	Oral use: For supportive treatment of cough, bronchitis and inflammation of the mouth and pharynx Unproven use: in folk medicine is used internally for bronchial catarrh, gastroenteritis, bladder complaints Topical use: topical treatment of wounds. Externally is used as a poultice and bath additive	Oral use: 1.5–2 g of comminuted drug is added to cold water and boiled or scalded and strained after 10 minutes Drink 2-3 times daily Daily dose: the average daily dose is 5 g of the drug. Duration of use: No restriction	Gruenwald *et al*. 2000

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
	for wound treatment.		
Mallow flowers	Use as: demulcent, anti-inflammatory, expectorant, emollient, pectoral	Oral use: 1.5 g flower per cup water; up to 5 g flower per day	Duke 2002
Mallow flower	Coughs and bronchitis Inflammations of the mouth and throat	Herbal tea: Place 1.5-2 g of the finely chopped herb in cold water, bring to a boil and remove from heat, or pour boiling water onto the herb. Steep for 10 minutes, then strain. Dosage: One cup, 2-3 times a day. Daily dose: 5 g	Kraft and Hobbs 2004
Malvae flos	Dry cough; irritation of the oral, pharyngeal or gastric mucosa	Internal use: Adult dose: 1.5-2 g of the drug as an aqueous cold macerate or hot infusion, repeated if required up to a daily dose equivalent to 5 g of the drug External use: As a gargle, a 5% decoction Duration of use: no restrictions. If symptoms persist or worsen, medical advice should be sought.	ESCOP Monographs 2009
Malvae sylvestris flos	Cough, bronchitis, inflammation of the mouth and pharynx. Traditionally for gastroenteritis, bladder complaints, wound management	Herbal tea: Average daily dose: 5.0 g of the drug, drink 2-3 times daily	Spiteri 2011
Malvae sylvestris flos	Oral use Topical use as a gargle	Single dose: 2 g for a cup. Daily dose: 2–3 cups Gargle: 1.5% as infusion	Haffner *et al*. 2016

Table 3. Overview of historical data. The traditional use and indications for *Malva sylvestris* L. leaves in the following handbooks:

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Malvae sylvestris folium	Herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough. Mucilaginous, expectorants, emollient	2–3 teaspoons of mallow leaves (3.2-4.8 g) in cold water daily 1/2 spoon of the "teep" preparation (50% of mallow leaf) 3 times daily Used also as a gargle	Madaus 1938
Folia malvae	As mucilaginous, mild astringents in inflammation angina and gastroenteritis In folk medicine for treatment of wounds	Oral and topical use as infusion or decoctum. Single dose: 0.5–1 g for a cup. Daily dose: 5 g. –Hung VI: 1.5 g per 1 cup as infusion or decotion–ÖAB 9	Kern *et al.* 1976
Malvae folium	As demulcent in irritations of the mucous membrane of the mouth and throat, and the associated dry cough. Used also as a mild astringent in angina or gastrointestinal inflammation. In folk medicine externally in a form of poultices for treatment of wounds	Herbal tea: 1.5–2 g of comminuted drug is placed in of cold water, and boiled for a short time, or boiling water is poured over it. It can also be used as a macerate (5-10 hours). Drink 1 cup several times daily Additionally, a reference to German Standardzulassung with the following posology is made: boiling water (ca. 150 ml) is poured over 3–5 g of mallow leaves and after 10–15 minutes is passed through a tea strainer. The tea can also be prepared with cold water and allowing it to drain for 2–3 hours with occasional stirring.	Wichtl, 1984

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
		A cup of tea is drunk several times during the day and in the evening before going to sleep.	
Malvae folium	To alleviate irritation of inflamed mucous membranes in mouth and throat and also in the gastrointestinal tract; catarrh of the upper respiratory tract	3–5 g is placed in cold water and boiled for a short time, or boiling water is poured over it, and after 10 minutes strained. Cold extracts (5-10 hours). Drink 1 cup several times daily	Wichtl 1994
Malvae folium	A mouth and pharyngeal irritations and associated dry cough. May be used as gargle	Oral use: 3–5 g (2 teaspoons = 0.5 g) of is added to 150 ml of boiling water and strained after 10-15 minutes. Alternatively, in cold water for 2–3 hours. Daily dose: 5 g	Hänsel *et al*. 1994
Dried Malvae sylvestris leaf	Oral use: For treatment of cough, bronchitis and inflammation of the mouth and pharynx Topical use: treatment of wounds. Unproven use: in folk medicine is used as poultices and bath additives for wounds	Oral use: to prepare infusion 3–5 g (about 2 teaspoons) of comminuted drug is added to boiling water and leave to draw for 2 to 3 hours; stir occasionally. Drink 2-3 times daily Daily dose: the average daily dose is 5 g of the drug Duration of use: No restriction	Gruenwald *et al*., 2000
Mallow leaves	Use as: anti-inflammatory, astringent, demulcent, expectorant, emollient	Herbal tea: 3–5 g per cup 2–3 times a day or 3.2–4.8 g in cold tea	Duke 2002

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Dry leaves of *Malva sylvestris* L. and/or *Malva neglecta* W.	Indications: cough and bronchitis Inflammation of the mouth and throat	Herbal tea: steep 3–5 g of the herb (ca. 2 teaspoons) in 150 ml of boiled water for 10 to 15 minutes, or place the herb in cold water and steep for 2-3 hours while stirring occasionally. Dosage: one cup, 1-2 times a day Daily dose: 5 g	Kraft and Hobbs 2004
Malvenblätter	Oral use Topical use as a gargle in inflammation of the mouth and throat and associated cough	Herbal tea: 1 teaspoon (ca. 1.8 g) of the leaves for the cup (150 ml), steep for 10–15 minutes Daily dose-3 cups	Standardzulassungen für Fertigarzneimittel. Band 2. 2011
Malvae folium	Oral use	Single dose; 3-5 g as herbal tea Adults: 2-3 times daily Children (1–4 years): 1 cup daily Children (4–10 years): 1-2 cups daily Children (10–16 years): 2 cups daily	Haffner *et al.* 2016

2.3. Overall conclusions on medicinal use

Traditional use of *Malva sylvestris*, L., flowers and leaves in the form of herbal tea is well documented in a number of literature sources. Aqueous extracts of the herbal substances are used in the Member States for at least 30 years. Based on information provided by the National Competent Authorities in the overview of the marketed products and literature data the following herbal preparations fulfil the criteria set in Directive 2001/83/EC for at least 30 years of the medicinal use:

Table 4: *Malva sylvestris* L. flowers-overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Flos Malvae	Traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough and in dyspeptic symptoms	Herbal tea: pour 1 L of boiling water over 10–15 g of flowers. Drink 2–4 glasses daily.	Muszyński *et al.* 1958
Flos Malvae	Oral use as demulcent in throat irritation	As decoction: ½ of tablespoon of flowers on 1 glass of water. Drink divided 2–3 times daily	Gobiec and Konieczny, 1967
Flores Malvae sylvestris	Oral use as mucilaginous, in inflammation of upper respiratory tract and throat and in gastroenteritis as mild astringents.	As infusion or decoction: 1.5 g on 1 teacup Single dose: 0.5-1 g Daily dose: 5 g For mouthwash 1.5% infusion	Kern *et al.* 1976
Flos Malvae	Traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough.	Herbal tea: pour 250 ml of boiling water over 1 table spoon crushed mallow flowers; drink 3 cups daily.	Ożarowski *et al.* 1978
Flos Malvae sylvestris	Protectivum, demulcens Oral use: traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough.	Herbal tea: pour 1–1½ glass of boiling water over 1–2 table spoons of flowers. Drink 1/3 of the glass 3 times daily. Used also for gargling in throat irritation	Ożarowski 1982

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Used in laryngitis, pharyngitis	In infants used as an enema.	
Malvae flos	Use: As demulcent in irritations of the mucous membrane of the mouth and throat, and the associated dry cough. Used also as mild adstringens in gastroenteritis	Oral use: 1.5–2 g in 150 ml of cold water, short boiling, steep for 10 minutes. 1 teaspoon=0.5 g Drink 1 cup several times daily.	Wichtl (editor), 1984; 1994
Malvae sylvestris L., flos	Traditional herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough	Herbal tea Oral use: 1.0 g of the comminuted herbal substance in 250 ml of boiling water as a herbal decoction Drink 2-3 times daily corresponding to the maximum daily dose of 3 g.	Poland (more than 30 years)

Table 5: *Malva sylvestris* L. leaves - overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Malvae Sylvestris folium	Herbal medicinal product used for treatment of the symptoms of oral or pharyngeal irritations and associated dry cough. Mucilaginous, expectorants, emollient	Daily dose: macerate prepared from 2–3 tea spoons of mallow leaf (3.2–4.8 g) in cold water, 1/2 spoon of the “teep” preparation (50% of mallow leaf) 3 times daily	Madaus 1938
Malvae folium	As mucilaginous, mild astringents in inflammation angina and gastroenteritis	Oral and oromucosal use as infusion or decoction. Single dose: 0.5–1 g for a cup.	Kern *et al.* 1976

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
		Daily dose: 5 g.	
Malvae folium	Oromucosal use: Inflammation of upper respiratory tract. As mild astringents in throat inflammation and gastroenteritis.	1.5-2 g finely cut drug pour with cold water and boil shortly, or boiling water pour over, and steep for 5-10 minutes. Also macerate (5-10 hours) is recommended. As bronchial tea more times a day 1 cup of tea	Wichtl (editor), 1984
Malvae sylvestris L., folium	Irritation of the mucous membrane in the mouth and throat and associated dry cough	Herbal tea: >12 years: Oral use: 1.8 g per 150 ml boiling water 3 times daily	Since 1986, DE

The following indications are proposed for the European Union Monographs on Malvae flos and Malvae folium:

Indication 1)

Traditional herbal medicinal product used as a demulcent preparation for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough.

Indication 2)

Traditional herbal medicinal product used as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort.

The topical use is mentioned in several literature sources (Hänsel *et al*. 1994; Gruenwald *et al*.2000; Kern *et al*. 1976); Wichtl 1984; 1994; Wurzer 1977) for treatment of wounds, skin inflammations, furuncles. Malvae flos and Malvae folium are described to be used in the form of poultices and/or as batch additive; however, no sufficient information on the preparations has been found.

Macerate preparation is mentioned in several literature sources. However, information on maceration time differs significantly. Taking into consideration risk of microbial contamination long maceration cannot be recommended and therefore macerate preparation is not included in the monograph. Although historically lower and higher posologies for comminuted herbal substance have been documented, the proposed posology reflects currently applied dosages.

Based on the literature data and information received from the Member States, the following posologies are suggested for comminuted herbal substance:

***Malva sylvestris* L. flos**

Oral use

Indication 1) and 2)

Adolescents, adults and elderly

1–2 g of the comminuted herbal substance in 250 ml of boiling water as a herbal infusion or in 250 ml of water as a decoction 2-3 times daily

Average daily dose: 5 g

Oromucosal use

Indication 1)

Adolescents, adults and elderly

Herbal tea: 1–2 g of the comminuted herbal substance in 250 ml of boiling water as a herbal infusion or in 250 ml of water as a decoction 2-3 times daily

Average daily dose: 5 g.

Malva *sylvestris* L. and /or Malva neglecta Wallr., folium

Oral use

Indication 1) and 2)

Adolescents, adults and elderly

1.8 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion or in 150 ml of water as a decoction 3 times daily.

Daily dose: 5.4 g.

Oromucosal use

Indication 1)

Adolescents, adults and elderly

Herbal tea: 1.8 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion or in 150 ml of water as a decoction 3 times daily.

Daily dose: 5.4 g.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

3.1.1.1. Antitussive effects

Flowers

- *In vivo experiment*

Mucilage and acidic polysaccharide fraction

In experiments performed by Nosalova *et al*. (2005) a mucilage and an acidic polysaccharide fraction (consisting of rhamnogalacturonan) isolated from mallow flowers (*Malva mauritiana*) were administered orally to cats at a dose of 50 mg/kg (without anaesthesia). Antitussive effect of the polysaccharides was evaluated by surgically implanted chronic endotracheal cannula into the trachea. It served not only to register the pressure on electromanometer but also to the irritation of the airway mucous membrane in the desired areas: laryngopharyngeal and tracheobronchial. These areas were five times stimulated mechanically with nylon fibre and then monitored prior to application of the tested substance as a control value and after 0.5, 1, 2 and 5 hours after the administration of the polysaccharides. Both mucilage and rhamnogalacturonan fraction significantly diminished the number of incidents of cough and its intensity (during inhalation and exhalation). Mucilage decreased frequency of cough, mostly in the laryngopharyngeal area, while the fraction of rhamnogalacturonan was effective in both areas, also in the trachea and bronchi and resulted in antitussive effects 15% higher than that of the mucilage. Moreover, only a rhamnogalacturonian fraction had an inhibitory effect on the maximum intensity of coughing. The effects of the application of mucilage rhamnogalacturonan fraction and reduction of the number of cough events were compared with the effect of non-narcotic peripherally acting antitussive drugs: prenoxdiazine (30 mg/kg), dropropizine (100 mg/kg) and the narcotic drug - codeine phosphate (10 mg/kg). Both mucilage substances have had greater inhibitory activity than prenoxdiazine and dropropizine but less than codeine. Depression of respiratory activity, typical of narcotic antitussive drugs was not notified during the experiments with *Malva sylvestris* mucilaginous substances.

3.1.1.2. Antiinflammatory effects

Flowers

- *In vitro experiments*

Water extract

Seiberg *et al*. (2006) tested the effect of the water extracts of Malvae sylvestris flower on enhancing production of the mucus. The authors described the effects of the extract on cell cultures transiently transfected the elastin promoter-luciferase reporter construct, driving the firefly luciferase gene. The extracts were added to the transfected cells and incubated for 48 hours. An increase in elastin promoter activity was observed in the presence of increasing doses of the extract (2.5% and 5%), as compared to untreated cells. Protection from metalloproteinase degradation was also investigated: Matrix Metalloproteinase-12 (MMP-12), also named human macrophage elastase activity was inhibited by water extract in a dose dependent manner. The concentration of the Malvae sylvestris extract as low as 0.6% resulted in approximately 23% reduction in MMP-122 activity, while 5% of extract inhibited MMP-12 activity for 80%. This shows that *Malva sylvestris* flowers water extract can protect elastin fibers from damage and degradation (Seiberg *et al*. 2006).

- *In vivo experiments*

Hydro-alcoholic extract

Nasiri *et a*l. (2015) studied activity of topical application of *Malvae sylvestris* flowers ethanolic extract on second degree burn injury and wounds in rats. Ethanol (70% V/V) was added to the powdered flowers and the hydroalcoholic extract of herbal flowers was dried afterwards to a powder to yield of 9.68% w/w. In experiment 5% and 10% *Malvae sylvestris* topical creams, normal saline (control) and standard silver sulfadiazine 1% were used in rats burned with hot metal plate. Wound area, percentage of wound contraction, and histological and bacteriological assessments were evaluated.

Malvae sylvestris cream significantly improved histological changes of tissue components in the process of healing when compared with silver sulfadiazine cream.

Water extract

Afshar *et al*. (2015) investigated the effects of topical administration of the mallow flowers aqueous extract on cutaneous wound healing in BALB/c mice. Experimental animals were divided into three groups: the first, second and third group received topical administration of *Malvae sylvestris* 1% water extract in cream, silver sulfadiazine topical cream and cold cream (positive and negative control groups), respectively. On days 4, 7 and 10 wound healing was evaluated histopathologically. On the 10^{th} day of the experiment, the *Malva sylvestris* treated mice showed significantly less fibrosis, less scar formation, and fewer hair follicles damage. The number of inflammatory cells in *Malvae sylvestris* and silver sulfadiazine-treated groups were significantly lower than in the control group.

Leaves

- *In vitro experiments*

Ethanolic extract

Ethanolic extract (obtained by mixing 1 part of herbal drug with 6 parts ethanol, for 7 days)of dried leaves of *Malva sylvestris* was tested for anti-inflammatory activity by Martins *et al*. (2014). In desferrioxamine-stimulated phorbol 12-myristate 13-acetate-differentiated culture of U937 cells influence of the *M. sylvestris* extract on release of the pro-inflammatory mediators prostaglandins PGE_2 and PGD_2 was measured. They mediate acute and chronic inflammatory responses associated with vasodilatation, fever, pain, and edema. U937-d cells are estimated as an appropriate model to mimic the oral cavity inflammations, against which *Malva sylvestris* is mainly used. U937-d cells were treated with *Malva sylvestris* ethanolic extract at 10.0 and 50.0 µg/mL. A significant dose-dependent reduction of PGE_2 and PGD_2 levels occurred using 10 µg/mL (10.74±2.86 and 9.60±6.89%) and 50 µg/mL of extract (48.37±3.24 and 53.06±6.15% respectively). The anti-inflammatory activity attributed to *Malva sylvestris* may be dependent on the reduction of prostaglandins as pro-inflammatory mediators.

Ethanolic, chloroform and ethyl acetate extracts

Benso *et al*. (2015) investigated anti-inflammatory activity of *Malva sylvestris* extracts in the model mimicking the periodontal structure infected by *Aggregatibacter actinomycetemcomitans.* An *in vitro* dual-chamber model to mimic the periodontal structure was developed, using a monolayer of epithelial keratinocytes and a subepithelial layer of fibroblasts. The periodontopathogen *A. actinomycetemcomitans* was applied to migrate through the cell layers and to induce the synthesis of immune factors and cytokines in the host cells. Ethanolic extract (prepared by mixing 8 parts of absolute ethanol) with 1 part of herbal drug and the lyophilized) (MSE) of the leaves of Malva sylvestris was successively partitioned using liquid-liquid extraction with hexane, chloroform and ethyl acetate. The final residue obtained after ethyl acetate fractionation was totally soluble in water and thus was called the aqueous fraction (AF). The extract (MSE), chloroform fraction (CLF) and aqueous fraction were resuspended in 1% ethanol and used in the biological assays. The extract minimum inhibitory concentration (MIC) 175 µg/mL, minimum bactericidal concentration (MBC) 500µg/mL and chloroform fraction (MIC 150 µg/mL, MBC 250 µg/mL) were found to have inhibitory activity against different odontopathogenic bacteria: *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Prevotella intermedia* and *Porphyromonas gingivalis*. The results shown that both MSE and CLF had inhibitory influence on the all four microorganisms tested. CLF was the most potent, and most effective in reducing the bacterial colonization ($p < 0.05$) with a MIC against *A. actinomycetemcomitans* of 150 µg/mL, a MIC against *F. nucleatum* of 500 µg/mL and a MIC against *P. intermedia* of 125 µg/mL. The

MSE had the lowest MIC against *P. gingivalis* (15.6 µg/ml compared to the positive control 10 µg/mL). Moreover, CLF promoted the down-regulation of genes IL-1beta, IL-6, IL-10, CD14, PTGS, MMP-1 and FOS as well as the reduction of the IL-1beta, IL-6, IL-8 and GM-CSF protein levels ($p < 0.05$).

- *In vivo experiment*

Water extract

Chiclana *et al*. (2009) studied topical antiinflammatory activity of *Malva sylvestris* L. leaves water extract on carragenin-induced hind paw oedema in rats. A decoction was prepared from 50 g of mallow leaves (yielding extract 50%). From this extract creams were prepared at 5, 10 and 20% v/w of the extract as a water-soluble cream base. A significative inhibition of edema was obtained with the 5% malva cream compared to placebo, and the effect of mallow extract was higher than that of a 2% indomethacin cream.

Hydroalcoholic extract and isolated compounds

Prudente *et al*. (2013) investigated the topical anti-inflammatory action of the hydroalcoholic extract of *Malvae sylvestris* leaves *in vivo* on a 12-O-tetradecanoylphorbol-acetate (TPA)-induced mouse ear oedema model in mice. Oedema was induced on the right ear by topical application of 2.5 µg perear of TPA dissolved in 20 µl of acetone. Hydroalcoholic extract of *Malvae sylvestris* leaves (0.001–3.0 mg perear), malvidin 3,5-glucoside (0.0004–0.1 µmol perear), malvidin 3-glucoside (0.0002–0.2 µmol perear) and dexamethasone (0.05 mg perear) which was used as a positive control. The extracts were dissolved in 2 µl of acetone and topically applied immediately after TPA. The thickness of the ears was measured before and 6 hours after induction of inflammation. Topical application of *Malvae sylvestris* hydroalcoholic extract inhibited ear inflammation and polymorphonuclear cells influx (myeloperoxydase activity-MPO) and interleukin-1b levels in the tissues. Malvidin 3-glucoside was also able to inhibit ear oedema and leukocytes. The oedema reduction induced by the *Malvae sylvestris* extract exhibited a mean ID_{50} value of 0.36 (0.14–0.90) mg per ear, with inhibition of 77±6% (3 mg perear), while malvidin 3-glucoside caused a reduction in oedema of 90±3% (0.2 µmol perear) and an ID_{50} value of 0.003 (0.002–0.004) µmol per ear. The extract inhibited TPA increase of myeloperoxydase activity in a dose dependent way: ID_{50}=0.46 (0.3–0.7) mg/ear and with inhibition of 73±1% (3 mg perear), the same as dexamethasone activity: 74±1% inhibition. Malvidin 3-glucoside (0.2 µmol perear) caused a reduction of 70±5% of MPO in the tissue. The increase in the level of IL-1β in the ear was inhibited in a dose dependent manner by topical application of hydroalcoholic extract from *Malva sylvestris*, presenting a mean ID_{50} value of 0.96 (0.92–1.0) mg per ear and 74.2% of inhibition at 3 mg per ear. The inhibitory activity of dexamethasone was similar. The authors conclude that hydroalcoholic extract from *Malva sylvestris* induces strong anti-inflammatory activity and probably malvidin 3-glucoside is responsible for this effects.

- *In vivo and in vitro experiments*

Water extract

El Ghaoui *et a*l. (2008) studied the influence water extract of *Malva sylvestris* leaves on antibody production in mice immunized with egg albumin. The effect of this extract on interleukin-4 (IL-4), interleukin -12 (IL-12) and γ-interferon gene transcription were investigated. The extract was prepared by heating the leaves in distilled water until boiling and left to cool at room temperature. The decoction was filtered and lyophilized and solution (50 mg/mL) was reconstituted using distilled water. Mallow extract had no effect on anti-egg albumin antibody production but enhanced IL-12 and γ interferon gene transcription. Authors conclude that *Malva sylvestris* extract promotes an inflammatory response

by induction of macrophages inducing them for production IL-12, which in turn activates Th1 lymphocytes which produce γ-interferon.

Aerial parts (flowers and leaves)

- *In vivo experiments*

Water extract

Sleiman and Daher (2009) investigated the aqueous extract of *Malva sylvestris* aerial parts in acute and chronic inflammation models induced by carrageenan and formalin in rats. Doses of 50, 100, 250 and 500 mg/kg b.w. of the extract were used orally for 1 month. Significant anti-inflammatory activity was observed at most doses used with an optimum inhibition at 100 mg/kg b.w. (60% inhibition) in both models. In other experiment protection against ethanol-induced gastric ulcer was evaluated. After administration of the *Malva sylvestris* aqueous extract at the dose of 500 mg/kg b.w. the maximum protection (37%) was obtained, a value significantly higher than that observed with a reference drug cimetidine (where it reached 30%).

N-hexane, ethanol and water extracts

Anti-inflammatory effects of different fractions of *Malva sylvestris* were evaluated in acetic acid–induced ulcerative colitis model in rats by Hamedi *et al*. (2016). A total of 200 g of powdered aerial parts was sequentially extracted with n-hexane, ethanol, and water (3x1 L and 48 hours for each) at room temperature. The fractions were concentrated by a rotary evaporator at 4^0C and dried applying a speed vacuum dryer or a freeze dryer and kept at -20^0C. Colitis in male rats was induced by rectal instillation of a 4% solution of acetic acid. Animals were divided into 8 experimental groups (6 in each) as follows: *Normal group*: without induction of colitis that received normal saline solution rectally at the day of induction. *Negative control group*: with induction of colitis that received distilled water orally. *Positive control group*: with induction of colitis that received prednisolone at dose 5 mg/kg perday orally prior to induction of colitis. *Treatment group I*: with induction of colitis that received aqueous fraction of *Malva sylvestris* at dose 200 mg/kg per day orally prior to induction of colitis. *Treatment group II*: with induction of colitis that received ethanolic fraction of *Malva sylvestris* at dose 200 mg/kg per day orally prior to induction of colitis. *Treatment group III*: with induction of colitis that received n-hexane fraction of *Malva sylvestris* at dose 200 mg/kg perday orally prior to induction of colitis. *Treatment group IV*: with induction of colitis that received the isolated polysaccharide of *Malva sylvestris* at dose 200 mg/kg per day orally prior to induction of colitis. In groups I to IV treatment was performed for 5 days consecutively before induction of colitis. *Treatment group V*: with induction of colitis that received the isolated polysaccharide of *Malva sylvestris* at dose 200 mg/kg per day orally for 5 days after induction of colitis. Twenty-four hours after the last dose of the drug in treatment group V and 24 hours after induction of colitis in other groups, rats were subjected to autopsy. Macroscopic and microscopic evaluation of colitis showed that the aqueous fraction was very effective in preventing the inflammation and therapeutic effectiveness was lower for ethanolic and n-hexane fractions. Polysaccharide was effective in pretreatment reducing signs of inflammation.The protective effect of the water fraction of *Malva sylvestris* on reduction of microscopic and macroscopic parameters of colitis was significantly higher than prednisolone. Anti-inflammatory effects of the tested fractions in this study seem to be related to their polysaccharide and polyphenol content.

Table 6. Overview of the main non-clinical data/conclusions- *Malvae flos*

Herbal preparation tested	**Strength Dosage Route of administration**	**Experimental model** ***In vivo / In vitro***	**Reference** **Year of publication**	**Main non-clinical conclusions**
1. mucilage 2. acidic polysaccharide fraction	50 mg/kg	*In vivo* in cats Model of cough stimulated by mechanical irritation of the larynx and trachea	Nosalova *et al*. 1994	Both tested substances significantly diminished the number of incidents of cough and its intensity. Mucilage decreased frequency of cough, mostly in the laryngopharyngeal area, while the rhamnogalacturonan fraction was effective in the trachea and bronchi (antitussive effects 15% higher than the mucilage). Both tested substances have had greater inhibitory activity than prenoxdiazine and dropropizine but less than codeine
Water extract	A) 2.5% and 5% B) 0.6% up to 5.0%	*In vitro* A) Induction of elastine production B) Inhibition of activity of matrix metalloproteinase-12	Seiberg *et al*. 2006	An increase in elastin promoter activity was observed in the presence of increasing doses of the extract (2.5%-1.93±0.33 and 5%-2.27±0.03), as compared to untreated cells: Matrix Metalloproteinase-12, (MMP-12), was inhibited by the extract in a dose dependent manner. Malvae sylvestris extract 0.6% resulted in approximately 23% reduction in MMP-12 activity, while 5% of extract induced inhibition of MMP-12

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo* / *In vitro*	Reference Year of publication	Main non-clinical conclusions
				activity for 80%.
Hydroalcoholic dry extract	Topical use 1) 5% and 10% in cream 2) Sulfadiazine topical cream 1% (positive control) 3) Saline (negative control)	*In vivo*: second degree burn injury and wounds in rats	Nasiri *et al*. 2015	M. sylvestris cream (5% and 10%) significantly improved histological changes of tissue components in the process of healing (scores: 35 and 39 respectively) compared with silver sulfadiazine cream (score 22).
Malva sylvestris, flos Water extract	Topical use 1) 1% in cream 2) Sulfadiazine topical cream 1% (positive control) 3) cold cream Saline (negative control)	*In vivo*: cutaneous wound healing in BALB/c mice	Afshar *et al*. 2015	There was less inflammation in the M. sylvestris-treated mice than other groups. The extract caused improvement of the wound healing process, connective tissue formation and re-epithelization. The Malva-treated mice showed less fibrosis and scar formation, and also fewer hair follicles were damaged in this group. The numbers of inflammatory cells in M. sylvestris and silver sulfadiazine-treated groups were significantly lower than in the control group.

Table 7. Overview of the main non-clinical data/conclusions- *Malvae folium*

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo* / *In vitro*	Reference Year of publication	Main non-clinical conclusions

Ethanolic extract (1:6 w/v)	10 and 50 µg/mL	*In vitro*	Martins *et al*. 2013	A significant dose-dependent reduction of PGE_2 and PGD_2 levels occurred for 10 µg/mL (10.74±2.86 and 9.60±6.89%) and 50 µg/mL of extract (48.37±3.24 and 53.06±6.15%).

Table 8. Overview of the main non-clinical data/conclusions- *Malvae flos and folium* (aerial parts)

Herbal preparation tested	**Strength Dosage Route of administration**	**Experimental model** ***In vivo/ In vitro***	**Reference** **Year of publication**	**Main non-clinical conclusions**
Water extract	50 mg/kg 100 mg/kg 250 mg/kg 500 mg/kg b.w. Orally Duration: 1 month	*In vivo* 1) Acute carrageenan inflammation model in rats 2) Chronic formalin inflammation model in rats 3) Experimental protection against ethanol-induced gastric ulcer	Sleiman and Daher 2009	Significant anti-inflammatory activity was observed with maximal inhibition at 100 mg/kg (60% inhibition) in both models. In experimental protection against ethanol-induced gastric ulcer the water extract at the dose of 500 mg/kg b.w. induced the maximum protection (37%) which was significantly higher than that observed with a reference drug cimetidine (30%).
N-hexane, ethanol, and water extracts	4 treatment groups: 1) Water extract 200 mg/kg per day 2) Ethanol extract 200 mg/kg per day 3) n-hexane extract 200 mg/kg per day 4) isolated polysaccharide 200	*In vivo* Acetic acid–induced ulcerative colitis model in rats.	Hamedi *et al*. 2015	The protective effects of water and ethanolic extracts were significantly higher than prednisolone effects. Ulcers were not observed in rats treated with water and ethanolic extracts and the damage scores in these 2 groups were significantly lower than

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo / In vitro*	Reference Year of publication	Main non-clinical conclusions
	mg/kg per day Control groups: 1) Control group-saline 2) Positive control-prednisolone 5 mg/kg per day Oral use			in the other groups.

3.1.2. Secondary pharmacodynamics

3.1.2.1. Antimicrobial activity

Flowers

- *In vivo* experiment

Ethanolic extract

Delaveau *et al*. (1980) administered to mice intraperitoneally the dry ethanolic extract(no further detail) of Malva sylvestris flowers in a dose of 50 mg/kg b.w. and registered an increase of survival of mice infected with Escherichia coli. This effect is attributed by the authors to the stimulation of phagocytic activity.

Leaves

- *In vitro* experiment

Water extract

Quave *et al*. (2008 b) tested several italian plants, including *Malva sylvestris* for inhibition of growth and biofilms in methicillin-resistant *Staphylococcus aureus* (MRSA). Water extract of *Malva sylvestris* was made by boiling 1 g (plant material) in 50 ml water for 30 minutes. It was found, that biofilm formation by the water extract was inhibited at concentration of IC_{50}=32 µg/ml.

Aerial parts

- *In vitro* experiments

N-hexane, dichloromethane and methanolic extracts

Razavi *et al*. (2011) evaluated antimicrobial activity of *Malva sylvestris* n-hexane, dichloromethane and methanolic flower and leaves extracts using disk diffusion method. The antibacterial and antifungal activity of the extracts were estimated against *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus agalactiae*, plant pathogen *Erwinia carotovora* and against *Candida kefyr*, *Candida albicans*, *Aspergillus niger*, *Penicillium* sp., and *Sclerotinia sclerotiorum*. The MICs of the extracts against the test microorganisms were determined by the agar dilution method. It was found,

that both flowers and leaves of M. sylvestris methanol extracts exhibited high antibacterial activity. These effects were comparablewith effects of erythromycin, gentamycin and amphotericin.

Decoction, infusion and assisted microwave extraction

Mihaylova *et al.* (2015) studied different extracts of fresh *Malva sylvestris* assisted extraction leaves and flowers for their level of total phenolics, antimicrobial activity against Gram-positive, Gram-negative bacteria, molds and yeasts. Moreover, their antioxidant activities were investigated using various methodologies: ABTS (α, α-diphenyl-β-picrylhydrazyl radical scavenging activity of the ethanol extract against radical caption), DPPH (α, α-diphenyl-β-picrylhydrazyl radical scavenging activity), FRAP (ferric reducing antioxidant power-the change in absorbance owing to the formation of a blue coloured Fe (II) -tripyridyltriazine compound from colourless oxidized Fe (III) form), and CUPRAC (cupric reducing capacity) with use of Trolox as a standard and expressed as μM of Trolox equivalent (TE)/g fresh weight. Fresh leaves and flowers of *Malva sylvestris* were subjected of three different types of extractions: 1) decoction–extraction by boiling of the plant material for 30 min with distilled water; 2) infusion–extraction by boiling water and then pouring it over the plant material, allowing it to steep in the liquid for 20 minutes; 3) microwave assisted extraction –the experiments were performed with water as solvent. The extracts solutions were filtered before analyses. Antimicrobial activity against saprophytic and pathogenic microorganisms: Gram-positive (*Bacillus cereus*, *Staphylococcus aureus* ATCC 6538-P), Gram-negative (*Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 8739, *Salmonella sp*. (clinical isolate), *Proteus vulgaris*) bacteria, molds (*Aspergillus niger*, *Penicillium sp*., *Rhizopus sp*.) and yeasts (*Saccharomyces cerevisiae*) was determined with the agar diffusion tests. Both flowers and leaves showed antimicrobial activity against the tested microorganisms. The flowers were found to be more active against pathogenic microorganisms. None of the tested extracts showed antifungal activity.

Hydroalcoholic extract

Cogo *et al.* (2010) evaluated antibacterial activity several plants, including the hydroalcoholic extract of inflorescence and leaves of *Malva sylvestris* against eleven clinical isolates of *Helicobacter pylori* and two reference strains (*H. pylori* 26695 and J99). All the strains were previously evaluated against clarithromycin, amoxicillin, furazolidone, tetracycline and metronidazole. Disk diffusion test and determination of the miniumum inhibitory concentration were performed by the agar dilution method. Results demonstrated that the extracts obtained from *M. sylvestris* L. were capable of inhibiting the *in vitro* growth of *H. pylori* in the range of 0.625 to 5.0 mg/ml.

Chloroform, water and ethanolic extracts

Zare *et al.* (2012) studied *in vitro* the antibacterial and antifungal activity of chloroform, ethanol and water extracts of the total aerial parts of *Malva neglecta* and *Malva sylvestris*. Minimal inhibitory concentration (MIC) of *M. sylvestris* and *Malva neglecta* extracts were presented against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Proteus vulgaris*, *Aspergillus niger*, *Aspergillus fumigatus* and *Candida albicans*. Experiments showed that all extracts were active against *S. aureus, P. aeruginosa,* and *P. vulgaris*. The ethanolic extract had the highest antibacterial activity compared to other solvents.

Alcoholic extract

Malvae sylvestris antifungal activity was evaluated *in vitro* against cultures of strains of *C. albicans* (ATCC 40227), *C. tropicalis* (ATCC 13803) and *C. krusei* (ATCC 40147) (Cardoso *et al.* 2012). The minimum inhibitory concentration (MIC) of Malva sylvestris 20% tincture was estimated. As positive control Nystatin 100,000 UI/ml was used. *M. sylvestris* tincture shown MIC at 25 mg/ml for *C. krusei*

and 100 mg/ml for *C. albicans* and *C. tropicalis.* The authors concluded that antimicrobial activity of products based on *Malva sylvestris* support their clinical use in the formulations for mouthwashes.

- *In vivo* experiment

Hydroalcoholic extract

Hydroalcoholic extract of the aerial parts of *Malva sylvestris* (prepared using 2 g herbal substance to 118 g extraction solvent:ethanol 96% V/V) diluted with sodium chloride 0.9% was investigated for antifungal activity in female NMRI mice by Hajyani and Modaresi (2016). Groups of mice received an i.p. injection of 1×10^6 cfu/ml (colony-forming unit) once to induce infection of *Candida albicans* ATCC 1677. Treatment groups received ten i.p. injections of *Malva sylvestris* hydroalcoholic extract in 50, 100, 200 mg/kg doses for 20 days. Suspension of *Candida albicans* (1×10^6 cfu/ml) was injected between fifth and sixth injections of the extract. The study was carried out to investigate effects of *Malva sylvestris* extract on the number of viable fungal cells in a sample, plasma proteins and gamma interferon expression. Significant reduction in the amount of albumin in the three treatment groups was found. In turn, the amount of β-globulin in groups receiving 50 to 100 mg/kg of the *Malva sylvestris* extract was significantly increased. Similarly, the amount of gamma interferon for all three treatment groups was also significantly increased when compared to the control group. The authors conclude that *Malva sylvestris* is able to stimulate an immune cellular response.

3.1.2.2. Antioxidant activity

Aerial parts

- *In vitro* experiments

Water extract, isolated compounds

The antioxidant activity of *Malva sylvestris* water extract was evaluated by Della Greca *et al.* (2009) by its capability to neutralize anionic DPPH and superoxide anion radicals and to give rise to formation of a phosphomolybdenum complex. The analysis of the water extract by applying the different chromatographic techniques resulted in the isolation of eleven compounds: 4-hydroxybenzoic acid, 4-methoxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid, 4-hydroxycinnamic acid, ferulic acid, 2-hydroxydihydrocinnamate, scopoletin, N- trans-feruloyl tyramine, a sesquiterpene, (3R, 7E)-3-hydroxy-5,7-megastigmadien-9-one and (10E, 15Z)-9,12,13-trihydroxyoctadeca-10 15-dienoic acid. The isolated compounds were present in the range of 0.3 to 3 µg/g in *M. sylvestris*. The strongest antioxidant activities were noted for 4-hydroxycinnamic acid and a sesquiterpene, N- trans-feruloyl tyramine. Their antioxidant effects were significantly higher than showed by the positive standard, α-tocopherol. All metabolites presented an anion superoxide radical scavenging activity over 15% higher than tocopherol.

Ethanolic and acetone extracts

Beghdad *et al.* (2014) studied the constituents of the leaves, flowers, stems and seeds of mallow, *Malva sylvestris* L., as well as their antioxidant properties using *in vitro* methods. They used the ferric reducing antioxidant power (FRAP) assay, by scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and total antioxidant capacity (TAC) based on the reduction of molybdenum (VI) to molybdenum (V). The concentration of phenolic compounds was higher in the extracts isolated from leaves (24.123±0.718 mg of gallic acid equivalents/g dried weight) than in flowers (6.978±0.602 mg of gallic acid equivalents). Similarly, the total flavonoids content was 5.694±0.017 mg in the leaves and 0.170±0.033 mg in the flowers (expressed as mg rutin equivalent per 100 g dried weight).

Other authors also found a higher phenolic content in leaves than in flowers (Barros *et al.* 2010). The evaluation of the antioxidant activity by three methods, including DPPH free radical scavenging activity, ferric reducing antioxidant power (FRAP) and total antioxidant capacity (TAC) showed that ethyl acetate (AcOEt) and *n*-Butanol (n-BuOH) fractions of leaves have a highest values of antioxidant activity. Concerning DPPH inhibition (%), all the samples proved to have high antioxidant activities (between 98.52 and 62.01%) and the greatest EC_{50} (the plant extract concentration of extract necessary to decrease DPPH radical scavenging by 50%) obtained was that of extracts of flavonoids, especially ethyl acetate (AcOEt-EC_{50}=3.10 mg/ml) showing the highest value of antioxidant activities for almost all parts of the plant. Antiradical activity defined as $1/EC_{50}$ was for the leaves 0.059 and for the flowers 0.071%. At 750 µg/ml, the most potent reducing agents were the flavonoid extracts from AcOET (43.110%) and n-BuOH (32.671%) fractions of leaves. In the phosphor molybdenum assay, the extracts exhibited some degree of activity in a dose dependent manner. It was generally observed that AcOEt fraction was more active than the n-BuOH fraction with DPPH and FRAP method. Comparison showed a higher antioxidant capacity to reduce molybdenum (VI) to molybdenum (V) reported for AcOEt fraction of leaves (0.138±0.006 mg of equivalent of ascorbic acid (EAA/g) and n-BuOH fraction of flower (0.118±0.018 mg EAA/g). The ethanol has been more efficient compared to the acetone solvent for extraction of antioxidants from leaf parts of *M. sylvestris* L. The ethanolic fraction has a better capacity probably due to higher hydrogen-donating constituents extracted by the solvent. The authors are of the opinion that the increase in antioxidant activity may be explained by the increase of solvent polarity.

3.1.2.3. Other activities:

Acetylcholinesterase (AChE) inhibitory activity

Water extract and essential oil

Ferreira *et al.* (2006) tested *in vitro* several Portuguese plants for AChE inhibitory activity, including aerial parts of *Malva sylvestris*. Essential oil, ethanolic extract (16.13 mg/mg of dried ethanolic extract, ethanol concentration not specified) and decoction (5 g/100 ml boiled for 20 minutes) were tested for their activity towards acetylcholinesterase (AChE) and their antioxidant activity. Decoction of *Malva sylvestris* in concentration of 5mg/ml inhibited activity of AChE by 25±5.7%. The essential oil of aerial parts of *Malva sylvestris* in concentration of 0.1 mg/ml induced inhibition of AChE by 28.1±2.9%. Ethanolic extract did not had any inhibitory effect.

Antinociceptive activity

Esteves *et al.* (2009) evaluated *in vivo* the antinociceptive activity of the *Malvae sylvestris* leaves aqueous extract. Initially, the infusion of the leaves (10% w/v) was lyophilized yielding 2.4% of aqueous extract. Experiments were performed on mice with use of writhing test, formalin-induced pain test, capsaicin-induced pain test and hot-plate test. Intraperitoneal administration of 10 mg/kg b.w. the aqueous extract induced significant antinociceptive activity in writhing test (76.4% of inhibition) and inhibition of the neurogenic (61.8%) and inflammatory (46.6%) phases in the formalin model. In capsaicin-induced pain model, the aqueous extract was also effective with inhibition of 62.9%, but it did not cause significant activity against hot-plate model. The authors concluded that the results could suggest that the antinociception caused by aqueous extract is related to the inhibition of prostaglandins synthesis pathway cyclooxygenase and unrelated to the stimulation of the opioid receptors.

Cytotoxic activity

Kaileh *et al.* (2007) have shown *in vitro* no cytotoxicity of *Malva sylvestris* aerial parts extract (extracted with a mixture of dichloromethane and methanol, 1: 1, V/V) on murine fibrosarcoma L929sA cells.

Hepatoprotective activity

Hussain *et al.* (2014) studied *in vivo* the hepatoprotective effects of the whole plant methanol extract of *Malva sylvestris* L. against paracetamol hepatotoxicity in mice. The whole plant was washed and air dried.. Dried powder (almost 2 kg) was soaked in 6 L of 95% methanol and was kept on a shaker for 7 consecutive days. After that, the extracts were separated by filtration and concentrated at 40°C under reduced pressure by rotary evaporator. The desired concentrations were obtained by dissolving the extract in physiological saline. Silymarin (100 mg/kg) was used as a comparator to analyze therapeutic effects of *Malva sylvestris.* Two doses (300 and 600 mg kg) were administered i.p. for 7 consecutive days followed by i.p. injection with paracetamol (250 mg/kg). Paracetamol induced a significant increase of plasma levels of the liver enzymes as the liver damage markers: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin. The tested extract of *Malva sylvestris* significantly reduced elevated concentrations of the liver enzymes in a dose dependent manner. As a result of the autopsy and histopathological examination of the liver tissue, paracetamol-treated group showed macrophages, plasma cell infiltration, vacuolization and cell necrosis. Treatment with *Malva sylvestris* followed by paracetamol administration showed few binucleated cells while most cells were normal, with slight congestion, vacuolization, and infiltration and dose dependently restored normal histological pattern of the liver. In particular, hepatoprotective effect was observed at a dose of 600 mg/kg of the extract after which use no necrosis was evident.

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Available non-clinical data underline the plausibiliy of the traditional use of mallow flowers and leaves for the symptomatic treatment of oral or pharyngeal irritation, associated dry cough and gastroenteritis. The reported pharmacological effects are not considered contradictory to the oral and oromucosal traditional use of mallow preparations as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry cough and for symptomatic relief of mild gastrointestinal discomfort. None of the reported pharmacological studies constitute any cause for safety concern.

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

No data available.

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

3.3.1. Single dose toxicity

No data available.

3.3.2. Repeated dose toxicity

No data available.

3.3.3. Genotoxicity

No data available.

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

Conforti *et al*. (2008) evaluated the acute toxicity of the hydroalcoholic extracts of Mediterranean dietary plants, including *Malva sylvestris*. The Microtox acute toxicity test measures the decrease in light emission from the marine luminescent *Vibrio fischeri* bacteria when exposed to organic extracts. The test is applied in evaluating the toxicity of water soluble substances. The plant leaves were air dried and extracted with 70% aqueous ethanol through maceration (48 hours for 3 times) at room temperature. The received extract was dried under reduced pressure. Initially the extract in ethanol 70%, with a concentration of 1 mg/ml, was diluted with the diluent solution to obtain both sample concentration and organic solvent concentration no higher than 1%. It was found, that *Malva sylvestris*, hydroalcoholic extract showed bioluminescence inhibition values of 17.16% after 5 minutes and 17.32% after 15 minutes of incubation. According to the guidelines ISO (ISO 11348/3, 1998) a toxic sample shows an effect percentage greater than 20%. This means that the hydroalcoholic extract *of Malva sylvestris* does not show toxicity under the established limit.

3.3.8. Conclusions

No relevant data on single dose and repeated-dose toxicity are available. Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been found.

Due to lack of genotoxicity data, a list entry for Malvae flos and Malvae folium cannot be recommended.

3.4. Overall conclusions on non-clinical data

Despite of published non-clinical data on several activities of the extracts of Malvae flos, Malvae folium and aerial parts of *Malva sylvestris*, a direct correlation of these results (type of extract, route of administration, *in vitro* vs. *in vivo*) with the clinical situation is not possible. Results from relevant experimental studies are supportive for the traditional uses of the *Malva sylvestris* flower and leaves as an infusion/decoction for symptomatic treatment of oral or pharyngeal irritation, associated dry cough and mild gastrointestinal discomfort.

Specific data on pharmacokinetics and interactions are not available.

Relevant toxicological studies are not available.

Tests on genotoxicity, reproductive toxicity and carcinogenicity have not been found.

Oral administration and oromucosal use of mallow flowers and leaves infusions/decoctions can be regarded as safe at traditionally used small doses (maximum daily dose of 5 g for flowers and 5.4 g for leaves) and adequate duration of use.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available

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

No data available.

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Only one clinical study was found in the literature (Elsagh *et al.* 2015). Briefly, Elsagh *et al.* (2015) described a placebo-controlled randomized clinical trial in adult patients with functional constipation treated with *Malva sylvestris* flowers aqueous syrup. A total 110 patients participated and started the medication (55 in verum and 55 in placebo group). Preparation of the *M. sylvestris* flower syrup was done in the Herbal Medicine Laboratory of the Shahid Beheshti School of Pharmacy (Tehran, Iran). One liter of boiled water (100^0C) was added to 100 mg of dry flowers for 4 hours. The solvent was then removed under vacuum and sugar solution 50% was added to the extract (50 mg of the extract in each 1 cm^3 of the syrup). Herb-to-extract ratio was then 6:1. Patients in the verum group received treatment for 4 weeks, 1 g of extract perday equivalent to 10 cm^3 of the syrup twice daily (2-3 hours after breakfast and lunch). The frequency of defecation per week and frequency of hard stool, straining during defecation, sensation of incomplete evacuation, and manual maneuvers to facilitate evacuation

were rated. An improvement or worsening in each symptom was assessed (self-rated) at the end of therapy by telephone interview. The primary outcome of the study was the changes in defecation and constipation symptoms' frequency after treatment. Changes in stool consistency, overall self-reported improvement in symptoms after treatment, and adverse effects were estimated as the secondary outcome. Comparisons between the two groups were performed with the t-Test, Mann-Whitney U Test, and Chi-Square (or Fisher's Exact) Test. ANOVA with repeated measures test for assessing time effect, treatment effect, and interaction between time and treatment was used. All data were analysed on the intention-to treat rules. The author's reported that after 4 weeks treatment an increase in defecation frequency was observed ($F=18.8$, $p < 0.001$) and more decrease in frequency of all constipation symptoms ($F=16.5$ to 25.3, all p values < 0.001). The verum group experienced also more reduction in frequency of hard stool forms (45.4% vs. 9.1%, $p < 0.001$) and reported more improvement in all symptoms (all p values < 0.01) compared to placebo. Side effects occurred in a few patients from the verum group. In 4 patients diarrhoea has been seen, in 4 patients acid regurgitation was observed, 2 patients experienced nausea and individual patients seen worse constipation, epigastric pain, heartburn and urticaria.

Assessor comment: In the study by Elsagh *et al.* 2015, a *M. sylvestris* flower syrup preparation was administered to patients with constipation. There are no medicinal products with this herbal preparation used for the treatment of constipation on the EU market. Therefore, the study cannot be taken into consideration for the establishment of a well-establish use monograph.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no published clinical studies on Malvae folium or Malvae sylvestris flos where the active substances of the medicinal product have been in medicinal use within the EU for at least ten years. Well-establish use in accordance with Article 10a of Directive 2001/83/EC is considered not fulfilled for Malvae folium or *Malvae sylvestris* flos.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

Mallow leaves are traditionally used for food purposes in the countries of the Mediterranean basin: in Portugal, Italy and Turkey young leaves are eaten raw in a salad or are cooked as a vegetable. Unripe fruits are eaten raw (Prudente *et al*. 2013).

5.3. Adverse events, serious adverse events and deaths

In a placebo-controlled randomized clinical trial in adult patients with functional constipation treated with *Malva sylvestris* flowers aqueous syrup there were a few and moderate side effects. Out of 55 treated patients in 4 patients diarrhoea has been seen, in 4 patients acid regurgitation was observed, 2

patients experienced nausea and individual patients seen worse constipation, epigastric pain, heartburn and urticaria (Elsagh *et al*.2015).

Literature describes two cases of acute liver and kidney damage, after oral consumption of *Malva sylvestris* and *Malva sylvestris var. grandiflora*. In both cases, the patients ate the mallow as a meal, and the nature of organ damage was acute.

Fulminant liver failure and renal failure (Aktaş *et al*. 2014) were reported as fatal in a 36-year-old female patient . Laboratory findings at admission were as follow: aspartate aminotransferase 1750 IU / mL (control<40 IU/mL), alanine aminotransferase 2200 IU/mL (control <40 IU/mL), alkaline phosphatase 400 IU/mL (control<240 IU/mL), gammaglutamyl transpeptidase 75 IU/mL (control<38 IU/mL) albumin 2.9 g/dL, total bilirubin 4.2 mg/dL, and direct bilirubin 2.8 mg/dL. Prothrombin time was prolonged to 18 seconds.

The case of liver injury associated with *Malva grandifolia* in 59-year-old woman with a medical history of hypertension was described by Ekiz *et al.* (2010). The woman with history of dyspepsia and long term hypertension treatment drunk *Malva grandifolia* juice (250 ml per day) for 4 weeks to control dyspeptic symptoms. Her laboratory data were as follows on admission: was notable for liver injury with aspartate aminotransferase 234 IU/ml (control<40 IU/ml), alanine aminotransferase 269 IU/ml (control<40 IU/ml), alkaline phosphatase 335 IU/ml (normal<240 IU/ml), and gamma-glutamyl transpeptidase 66 IU/ml (control<38 IU/ml) and testify to liver damage. Albumin, bilirubin, and prothrombin time were normal. After stopping drinking the juice, liver enzymes normalized quickly and were within normal limits after 10 days from admission.

In both above mentioned case reports the exact amount of mallow consumed as a vegetable was unknown, detailed species were not precisely specified, and the clinical toxicological diagnosis is missing. The causal relationship could not be confirmed.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Particular use in children has not been reported.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special Warnings and precautions for use

Indication 1)

If dyspnoea, fever or purulent sputum occurs during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Indication 1) and 2)

The use in children and adolescent under 12 years of age has not been established due to lack of adequate data.

5.5.4. Drug interactions and other forms of interaction

No data available.

5.5.5. Fertility, pregnancy and lactation

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

No fertility data available.

5.5.6. Overdose

No case of overdose has been reported.

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

No studies on the ability to drive or operate machinery have been performed.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Recently, scientific literature describes two cases of poisoning of mallow consumed as food. However, there is no scientific confirmation of its toxicity when used in specified strength/posology and route of administration in the therapeutic indications proposed in the European Union monograph. The experimental toxicological data are limited but given the history of long-term and present use in humans, also as food, it seems that there are no safety concerns for the oral or oromucosal use of preparations of common mallow.

6. Overall conclusions (benefit-risk assessment)

There are no published clinical studies on Malvae folium or Malvae sylvestris flos where the active substances of the medicinal product have been in medicinal use within the EU for at least ten years. Well-establish use in accordance with Article 10a of Directive 2001/83/EC is considered not fulfilled for Malvae folium or Malvae sylvestris flos.

The traditional medicinal use of mallow flowers and leaves has been documented in several medicinal handbooks with indications consistent with the existing pertinent pharmacological experiments performed *in vitro* and *in vivo* and it is substantiated by the presence of medicinal products on the European market.

The traditional use of mallow preparations (*Malva sylvestris* L., flos and *Malva sylvestris* L., *Malva neglecta* Wallr. or a mixture of both species, folium) fulfils the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2001/83/EC as amended. All the requirements for traditional use (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety) are met.

The relevant toxicological data are not available but given the history of long-term and present use in humans, also as food, it seems that there are no safety concerns for the oral or oromucosal use of preparations of common mallow in the doses proposed in the monograph.

The following indications and posologies are proposed for the European Union monographs:

***Malva sylvestris,* L., flos**

Indication 1) Traditional herbal medicinal product used as a demulcent preparation for the symptomatic treatment of oral or pharyngeal irritation, associated dry cough

and

Indication 2) Traditional herbal medicinal product used as a demulcent preparation for the for the symptomatic relief of mild gastrointestinal discomfort.

Posology for adults and adolescents over 12 years: single dose: 1-2 g of the comminuted herbal substance in 250 ml of water as a herbal tea for oral use (indication 1 and 2) or as a herbal infusion or as a decoction for oromucosal use 2–3 times daily (indication 1); average daily dose: 5 g.

***Malva sylvestris L.* and/or *Malva neglecta* Wallr., folium**

Traditional herbal medicinal product used as a demulcent preparation for the symptomatic treatment of oral or pharyngeal irritation, associated dry cough and for the symptomatic relief of mild gastrointestinal discomfort.

Posology for adults and adolescents over 12 years: single dose: 1.8 g of the comminuted herbal substance in 150 ml of water as a herbal tea for oral use (indication 1 and 2) or as a herbal infusion or as a decoction for oromucosal use 3 times daily (indication 1); daily dose: 5.4 g.

The therapeutic areas for browse search with traditional use indications are: 'cough and cold' and 'gastrointestinal disorders'.

As a general precaution related to the therapeutic indication for symptomatic treatment of oral or pharyngeal irritation, associated dry cough and gastrointestinal discomfort, the product information should include a warning text advising the patient to consult a doctor or a qualified health care practitioner if the symptoms worsen or persist longer than 1 week during the use of the product for indication 1) and 2 weeks for indication 2).

Malvae flos and Malvae folium cannot be recommended for oral use in children under 12 years of age due to lack of adequate data.

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 data on fertility is available.

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

Tests on genotoxicity, reproductive toxicity and carcinogenicity are not available. A European Union list entry is not supported due to lack of data on genotoxicity.

Annex

List of references