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EMA/HMPC/560906/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Chamaemelum nobile* (L.) All., flos

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Chamaemelum nobile* (L.) All., flos
Herbal preparation(s)	a) Comminuted herbal substance b) Liquid extract (DER 1:1), extraction solvent ethanol 70% v/v
Pharmaceutical form(s)	Herbal substance and comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage forms for oral use.
Rapporteur	Dezső Csupor
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1. Introduction

Chamaemelum nobile (L.) All. (syn. *Anthemis nobilis* L.; *Anthemis odorata* Lamk.; *Chamaemelum odoratum* Dod.; *Chamomilla nobilis* God.), the so-called Roman chamomile, is a perennial herb of the *Asteraceae* family. It is native to Southwest Europe (France, Spain and Portugal) but the plant is present all over Europe, North Africa and Southwest Asia. The plant is cultivated mainly in England, Belgium, France, Germany, Hungary, Poland, Bulgaria, Egypt and Argentina.

Roman chamomile reaches a height of 15 to 30 cm and generally flowers from June to September. As a result of breeding, some of the tubular florets present in the wild plant have become ligulated, and this "double" or "semi-double" flower head forms the commercial drug. This variety (cultivar) is known since the 18th century, it is sterile and propagated vegetatively by suckering (Fauconnier *et al.*, 1996). The white to yellowish-white flower heads are 2-3 cm in diameter and have 2-3 rows of erect, imbricate, pale green, narrowly lanceolate, membranaceous, involucral bracts. Female ray-florets, up to 7 mm long, have more or less four parallel nerves, an irregular three-toothed tip and a short, yellowish-brown ovary (achene). In the centre of the flower-head, there are few disk-florets but these may also be entirely absent. The base of the conical receptacle is covered with numerous oblong scales (paleae) (Bisset, 1994).

Although the Commission E did not approve Roman chamomile flower for an evidence-based phytotherapeutic application (Blumenthal *et al.*, 1998), the herbal substance is listed and described in several pharmacopoeias and stated to possess carminative, anti-emetic, antispasmodic and sedative properties (Barnes *et al.*, 2002). It has been used for dyspepsia, nausea and vomiting, anorexia, vomiting of pregnancy, dysmenorrhoea and specifically for flatulent dyspepsia associated with mental stress (Bisset, 1994) (Bradley, 1992).

Roman chamomile is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that Roman chamomile can be added to foodstuffs in small quantities with a possible limitation of an active principle (as yet unspecified) in the final product (Barnes *et al.*, 2002). Chamomile is commonly used as an ingredient of herbal teas. Previously, Roman chamomile has been listed as GRAS (Generally Recognised As Safe) (Leung, 1980) by the FDA. Most GRAS substances have no quantitative restrictions as to use, although their use must conform to good manufacturing practices. In the case of roman chamomile, no restriction is noted (FDA, 2010).

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

- Herbal substance(s)

Dried flowers of the cultivated double flowered variety of *Chamaemelum nobile* (L.) All. (syn. *Anthemis nobilis* L.) [Fam. *Asteraceae*]. It contains not less than 7 ml/kg of essential oil. (Ph. Eur. 6, 2008)

Dried flower heads of the cultivated double variety of *Chamaemelum nobile* (L.) Allioni (*Anthemis nobilis* L.), Compositae[1] (Bradley, 1992).

- Herbal preparation(s)

- Comminuted herbal substance

- Liquid extract (DER 1:1, 70% ethanol) (Bradley, 1992) (British Herbal Pharmacopeia, 1974)

- Tincture (DER 1:5, 45% ethanol) (Bradley, 1992)

[1] Alternative name for the official term Asteraceae

- 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.

- Constituents

Constituents derived from the flower

Volatile oil
Roman chamomile flowers contain 0.6-2.4% volatile oil (Zwaving, 1982). The composition of the oil is complex, up till now more than 140 components have been identified (Fauconnier *et al.*, 1996). In the oil the proportion of low molecular weight esters is high, which are synthesized by the esterification of a series of aliphatic C_3-C_6 alcohols such as n-buthanol, iso-buthanol, iso-amylacohol, and 3-methyl-pentan-1-ol with angelic acid, tiglic acid, metacryl-, n- and isobutyric, propionic and acetic acid (Zwaving, 1982) (Nano *et al.*, 1976) (Klimes and Lamparsky, 1984). The main constituents of the volatile oil are 36.0-25.85% iso-butyl angelate, 23.7-10.9% iso-amyl iso-butyrate, 20.3-13.0% 2-methylbutyl angelate, 19.9-11.7% iso-amyl tigliate, 12% propyl tigliate, 5.3-17.9% iso-amyl angelate and 3.7-5.3% iso-butyl iso-butyrate (Chialva *et al.*, 1982) (Antonelli and Fabbri, 1998) (Balbaa *et al.*, 1975) (Omidbaigi *et al.*, 2003) (Omidbaigi *et al.*, 2004) (Inouye *et al.*, 2006) (Tognolini *et al.*, 2006). Furthermore, the oil contains 4% monoterpene such as α- and β-pinen, β-myrcene, limonene, γ-terpinene, p-cymene, camphene, (-)-pinocarvone and (-)-*trans*-pinocarveol; and 1.54% sesquiterepene derivatives including β-selinene, humulene, α- and β-cubene, α- and β-caryophyllene, chamazulene, farnesene, cadinen, bisabolane and bisabolene (Fauconnier *et al.*, 1996) (Zwaving, 1982) (Laurelle, 1959) (Chialva *et al.*, 1982) (Duarte *et al.*, 2005) (Inouye *et al.*, 2006) (Tognolini *et al.*, 2006). According to Duarte *et al.*, (2005) the essential oil contains 4.18% bisabolene.

Sesquiterpenes (bitters)
0.6% of sesquiterpene lactones of the germacranolide type (Wichtl, 2004). Sesquiterpene lactones of germacranolide type including nobilin, 3-epinobilin, 1.10-epoxynobilin, 3-dehydronobilin and hydroxyisonobilin have been identified (Holub and Samek, 1977) (Benesova *et al.*, 1964) (Grabarczyk *et al.*, 1977) (Samek *et al.*, 1977) (Zwaving, 1982) (Benesova *et al.*, 1970) (Barbetti and Casinovi, 1981).
Anthecotulide, a sesquiterpene lactone with an exocyclic methylene group having high sensitizing potential was described in *A. cotula* (Franke and Schilcher, 2005), but there is no report in the literature regarding its presence in *A. nobilis*.
Nobilin and its derivatives are the potential contact allergens of the plant; however this is not confirmed experimentally. In one case report the epicutaneous test was negative for sesquiterpene lactones, however positive for bisabolol. The sensitization capacity of Roman chamomile is moderate (Hausen and Vieluf, 1997).

Hydroperoxides
1β-Hydroperoxyisonobilin, allylhydroperoxides have been identified from the ethanolic extract of the drug (Rucker *et al.*, 1989) (Mayer and Rucker, 1987).

Flavonoids
Roman chamomile flowers contain 0.5% flavonoids, mainly in glycosidic form. Anthemoside (apigenin-2,3-dihydorycinnamoyl acid 7-O-β-D-glucose), cosmosiosid (apigenin 7-O-β-D-glucose), apiin (apigenin 7-O-β-D-apiosylglucoside) and chamaemeloside [apigenin 7-O-β-D-glucose-6″-(3″′-hydroxy-3″′-methyl-glutarate)], luteolin 7-O-β-D-glucose, quercetin 3-O-α-L-rhamnoside and kaempferol. The free aglycons were detected only in damaged flowers after drying (Herisset *et al.*,

1970) (Herisset *et al.*, 1973) (Klimes and Lamparsky, 1984) (Chaumont, 1969) (Zwaving, 1982), (Herisset *et al.*, 1971) (Abou-Zied and Rizk, 1973) (Pietta *et al.*, 1991) (Tschan *et al.*, 1996).

Catechins
Catechins are responsible for the browning of the flowers during drying (Herisset *et al.*, 1970) (Zwaving, 1982).

Coumarins
Scopolin (7-β-D-glucopyranosyl-scopoletin), umbelliferone, herniarin and, in the well dried drug, scopoletin has also been identified (Chaumont, 1969) (Zwaving, 1982) (Abou-Zied and Rizk, 1973) (Leung, 1980).

Polyacetylenes
Cis- and *trans*-spiroether derivatives have been detected in the flowers of Roman chamomile (Ma *et al.*, 2007).

Phenolic acids
The glucose esters caffeic acid, ferrulic acid and anthenobilic acid were identified in the drug. In the fresh and carefully dried flowers, only the *trans*-caffeic acid-glucose ester was detected, whereas in the damaged flowers the *trans*- and *cis*- forms of the caffeic acid are accumulated (Chaumont, 1969) (Herisset *et al.*, 1974).

Triterpenes and steroids
Roman chamomile flowers contain anthesterols, β-amyrin, taraxasterol, pseudotaraxasterol, β-sitosterol (Zyczyńska-Baloniak *et al.*, 1971) (Fauconnier *et al.*, 1996).

Polysaccharides
From the aqueous extract of Roman chamomile flowers and herb acidic polysaccharides were isolated. The polysaccharide content of the dried flower is 3.9%, whereas 1.0% of the dried herb (Lukacs, 1990).

The main constituents of Roman chamomile flower are depicted in Figure 1.

Constituents derived from other plant parts

From the ethanolic extract of the leaves of Roman chamomile, a sesquiterpene lactone, hydroxyisonobiline (Grabarczyk *et al.*, 1977) (Samek *et al.*, 1977) has been identified, whereas from an apolar extract of the root (ether-petrolether 1:2, v/v) polyacetylenes, including *cis*- and *trans*-dehydromatricariaester and tiophenesetrs have been identified (Bohlmann *et al.*, 1962) (Bohlmann and Zdero, 1966) (Bohlmann *et al.*, 1973).

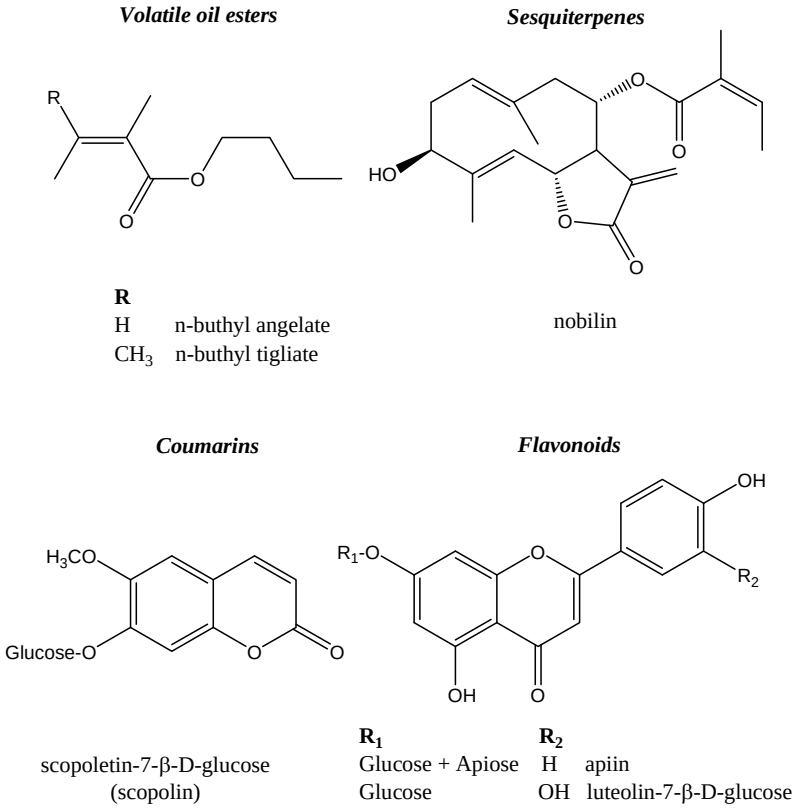

Figure 1. Main constituents of Roman chamomile flower

1.2. Information about products on the market in the Member States

Austria

The herbal substance is only available in multicomponent herbal teas.

Germany

The herbal substance is only available in combination products.

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or

Member State	Regulatory Status				Comments
					authorized products
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combination
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorized products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Databases Science Direct, SciFinder, Pubmed and Web of Science were searched using the terms [Chamaemelum nobile], [Roman chamomile] and [Anthemis nobilis]. Handbooks and textbooks on the topic were also used.

Data concerning *Matricaria recutita*, German or Hungarian chamomile were excluded.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The name *Chamaemelum* was first used by Dioscurides (Hiller and Melzig, 1999). However, according to Evans (1989), it has proved impossible to trace back the plant and herbal substance in classical writings, because of the large number of similar *Asteraceae* plants.

Roman chamomile is known as a medicinal plant since the middle ages. The name Roman chamomile was first bestowed upon the plant by Joachim Camerarius in 1598, after observing it growing abundantly near Rome (Abramson *et al.*, 2010). The European cultivation of the plant started in England in the 16th century (Hiller and Melzig, 1999). The plant obtained the name "nobile" (Latin, noble) because of its therapeutic properties, which were stated to be better than those of the German chamomile (Hiller and Melzig, 1999). The double variety of the flower, which serves now as the main commercial herbal substance, was certainly known in the 18th century (Evans, 1989). The plant was listed first in the 1741 Pharmacopoeia of Württenberg as a carminative, painkiller, diuretic and digestive aid (Lukacs, 1990).
Augustin *et al.* (1948) mention Chamomillae romanae flos as a herbal substance applied both internally (dyspeptic complaints, symptoms associated with menstruation) and externally (skin problems). In the book of Rápóti and Romváry (1974), the application of the herbal substance to relieve dyspeptic complaints and flatulence is cited.
Chamomillae romanae flos is included in the British Herbal Pharmacopoeia (BHP) published in 1974 (BHP, 1974) and in the British Herbal Compendium (BHC) Volume 1 published in 1992 (Bradley, 1992).
In the present times, Roman chamomile flower is an official herbal substance of several pharmacopoeias including the European Pharmacopoeia (Ph. Eur. 2008).

Type of tradition: European.

2.2. Information on traditional/current indications and specified substances/preparations

Roman chamomile–based preparations are used orally for the symptomatic treatment of gastrointestinal disorders such as epigastric bloating, impaired digestion, eructation, flatulence, and as an adjunct in the treatment of the painful component of functional digestive symptoms. Topically, it is an emollient and itch-relieving adjunct in the treatment of skin disorders and a trophic protective agent from cracks, abrasions, frostbites, chaps and insect bites. It may be used for an eye irritation or discomfort of various etiologies. Furthermore, uses as an analgesic in diseases of the oral cavity, oropharynx or both and as a mouthwash for oral hygiene have been documented (Bisset, 1994) (Bruneton, 1999). The uses of Roman chamomile that are described in the Commission E monograph (Blumenthal *et al.*, 1998) are similar: dyspepsia and inflammation of the mouth.
The herbal substance and its extracts are ingredients of colour-lightening shampoos (perhaps due to its peroxide content) (Bruneton, 1999).
Chamomillae romanae flos is included in the BHP 1974 and in the BHC 1992 with specified indications and posology. According to the BHC 1992, Chamomillae romanae flos has also been used in Belgium, France and Germany with specified indications at least since 1991, 1990 and 1986, respectively (Bradley, 1992).

For *Chamaemelum nobile* flos a period of at least 30 years of medicinal use, as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product, is fulfilled on the basis of the following references:

Herbal substance/ preparation	Indication	Reference	Tradition
Dried flowerheads	Dyspepsia; flatulent dyspepsia associated with mental stress.	BHP, 1974	since 1974
Liquid extract DER 1:1), extraction solvent ethanol 70% v/v	Dyspepsia; flatulent dyspepsia associated with mental stress.	BHP, 1974	since 1974

Less than 30 years of medicinal use is shown for the following preparation:

Herbal substance/ preparation	Indication	Reference	Tradition
Tincture (1:5 45%ethanol)	Dyspepsia.	BHC, 1992	since 1992

The evidence for a medicinal use for minor inflammations of the mouth and throat does not amount to at least 30 years as requested by Directive 2004/24/EC. Thus, despite availability of data on indications and posology on such use, it has been excluded from the monograph.

Herbal substance/ preparation	Indication	Reference	Tradition
Dried flowerheads	Inflammations of the mouth and throat	Standardzulassung No. 1069.99.99	since 1986

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

In the BHC1992), the indications and posology of Roman chamomile flower are as follows:
- Internally: dyspepsia, nausea, vomiting of pregnancy irritable bowel. Posology: dried flower heads, 1.5-3 g or in infusion, three times daily; 1.5-3 ml liquid extract (DER 1:1, 70% ethanol); 3-5 ml tincture (DER 1:5 45% ethanol)
- Topically: inflammations of the skin and oral mucosa, minor wounds and abrasions. Posology: as infusion in poultices or mouthwashes; semi-solid preparations containing 5-15% of the herbal substance or equivalent (Bradley, 1992).

According to Newall *et al.* (1996), the BHP published in 1983 contained the dried flowerheads of *Chamaemelum nobile* and a liquid extract of the herbal substance (DER 1:1, 70% ethanol). The posology of the herbal substance is 1-4 g by infusion three times daily and that of the liquid extract is 1-4 ml three times daily.

In the BHP published in 1974, dried flowerheads of *Chamaemelum nobile* and a liquid extract (DER 1:1, 70% ethanol) are included with the indications: dyspepsia and flatulent dyspepsia associated with mental stress. Dosage: thrice daily 1-4 g herbal substance by infusion or 1-4 ml of liquid extract thrice daily (BHP, 1974).

In Germany, according to the Standardzulassung No. 1069.99.99 (published 12.3.1986 for a standard medicinal tea), the labelling must include: Indications: Complaints such as bloatedness, flatulence and mild, spasmodic gastro-intestinal disorders; inflammations of the mouth and throat. Dosage instructions and mode of use: Pour hot water (ca. 150 ml) over a tablespoonful (2 to 3 g) of Roman Chamomile Flower and after about 10 minutes pass through a tea strainer. Unless otherwise prescribed, drink a cup of freshly prepared, warm tea 3 to 4 times daily between meals or use as a mouth and throat wash (Bradley, 1992).

In Belgium (according to Circulaire No. 367 of July 1991), the indications for this herbal substance must be stated as:

Traditionally used in the symptomatic treatment of digestive disorders, although its activity has not been proved in accordance with the current evaluation criteria for medicines.
Or:
Traditionally used topically as an emollient and/or antalgesic and/or antiseptic, although its activity has not been proved in accordance with the current evaluation criteria for medicines.
Or:
Traditionally used topically as a soothing and antipruriginous application for dermatological affections, although its activity has not been proved in accordance with the current evaluation criteria for medicines (Bradley, 1992).

In France, the uses of Roman chamomile flower reported in the Bulletin Officiel No. 90/22 bis are as follows:
- Traditionally used in the treatment of digestive disorders such as: epigastric distension; sluggishness of the digestion; belching; flatulence.
- Traditionally used as adjuvant treatment for the painful component of spasmodic colitis.
- Traditionally used topically as a soothing and antipruriginous application for dermatological ailments, as protective treatment for cracks, grazes, chaps and against insect bites.
- Traditionally used in cases of ocular irritation or discomfort due to various causes (smoky atmosphere, sustained visual effort, bathes in the sea or swimming pool etc.).
- Traditionally used topically (mouth and throat washes, pastilles) as an anodyne for affections of the buccal cavity and/or the oropharynx.
- Traditionally used topically in mouth washes, for oral hygiene (Bradley, 1992).

Additional dosages for administration (adults) for traditional uses recommended in standard herbal reference texts are given below.

Dried flowerheads

- 1–4 g as an infusion, three to four times daily (Barnes *et al.*, 2002) (Bisset, 1994).

- Preparation: To prepare a decoction, add 1-4 g drug to 100-150 ml water. An infusion is prepared using 7 to 8 capitula per cup (PDR, 2000).
- A 3% infusion is made for external use (Bisset, 1994).
- When used as a bath additive, add 50 g to 10 litres of water. Liquid rubs are applied as poultices or washes 2 to 3 times daily (PDR, 2000).

Liquid extract (1:1 in 70% alcohol)

- 1–4 ml, three times daily (Barnes *et al.*, 2002).

The Community herbal monograph refers to the following posology:

Herbal substance/ preparation	Posology	Reference	Tradition
Dried flowerheads	1-4 g as an infusion 3 times daily	BHP, 1974	since 1974
Liquid extract DER (1:1), extraction solvent ethanol 70% v/v	1-4 ml 3 times daily	BHP, 1974	since 1974

3. Non-Clinical Data

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

Pharmacodynamics

Anti-inflammatory effect

In view of the similar chemical composition, German and Roman chamomile are thought to possess similar pharmacological activities (Barnes *et al.*, 2002). Few studies have been conducted specifically for Roman chamomile, but the azulene compounds are reported to possess anti-inflammatory properties; their mechanism of action is thought to involve inhibition of histamine release (Barnes *et al.*, 2002) (Abramson *et al.*, 2010).

The anti-inflammatory effect of the polysaccharides isolated from the aqueous extract of Roman chamomile flowers and herb was tested with paw oedema test on Sprague-Dowley rats, where inflammation was generated with subplantar injection of viscarine. The flower and herb polysaccharides were administered by intraperitoneal (i.p.) route, in 10 mg/kg dose. Compared to an untreated control, the polysaccharides reduced the inflammation of the paw by 36.2 and 37.7%, respectively. In the same experiment, orally administered indomethacin showed 48.6% inhibition (Lukacs, 1990).

Anti-oedema effect

Anti-oedema effect of Roman chamomile essential oil was examined in the carrageenan-induced paw oedema test, in male Wistar rats. Intraperitoneal injection of 350 mg/kg volatile oil inhibited the oedema formation of the paw with 22.8-38.7% after 2 hours and with 38-43% after 3 hours. Indomethacin (5 mg/kg, i.p.) under the same conditions showed 73.7% and 66.7% inhibition, respectively (Rossi *et al.*, 1988) (Melegari *et al.*, 1988). Due to the high dosage, the results cannot be interpreted (Hänsel *et al.*, 1993).

Antimicrobial activity

The volatile oil showed an activity (filter paper diffusion test) against Gram-positive bacteria, especially *Bacillus subtilis*, *B. anthracis*, *Micrococcus glutamicus*, *B. sacchrolyticus*, *B. thuringiensis*, *Sarcina lutea*, *B. stearothermophilus*, *Lactobacillus plantarum*, *Staphylococcus aureus*, *Staphylococcus* sp. and *L. casei*, whereas the oil showed no activity against Gram-negative bacteria species including *Salmonella*

group B, *Citrobacter* sp., *Enterobacter* sp., *Escherichia coli*, *Pseudomonas* sp., *Salmonella saintpaul* and *Salmonella weltevreden*. The Roman chamomile volatile oil inhibited the growth of dermatophytons, *Alternaria* sp., *Aspergillus fumigatus* and *A. parasiticus*. In the same study, the volatile oil was inactive against *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Aspergillus niger* (Hänsel *et al.*, 1993).

According to Piccaglia *et al.* (1993), Roman chamomile essential oil possessed a moderate antibacterial activity, determined with agar diffusion method, against *Flavobacterium suaveolens*, *Clostridium sporogenes* and *Micrococcus luteus.*

Roman chamomile essential oil was moderately effective against Gram-positive and Gram-negative bacteria using a disk diffusion method. Moreover, the oil showed activity against *C. albicans* and *Rhizopus oligosporus*. In the same study, Roman chamomile oil was the most active against T_7 and SA phage viruses (Chao *et al.*, 2000).

A moderate activity of Roman chamomile flower essential oil against *C. albicans* (minimum inhibitory concentration MIC=0.8 mg/ml) was determined by microplate method, whereas the alcoholic extract of the plant was ineffective (Duarte *et al.*, 2005). A strong activity of Roman chamomile oil was detected against strains of Gram-positive (*S. aureus*, *Enterococcus faecalis*) and Gram-negative (*E. coli*, *Proteus vulgaris*, *Klebsiella pneumoniae* and *Salmonella* sp.) bacteria as well as against *C. albicans* using agar diffusion and agar dilution methods. The effect was attributed to both the main and minor ester constituents of the oil (Bail *et al.*, 2009).

A blended essential oil, containing Roman chamomile flower, ylang ylang, spruce and lavender oils showed potent activity against Methicillin-resistant *Staphylococcus aureus* determined with a disk diffusion assay. None of the tested oils showed significant activity when tested alone suggesting a synergistic effect of the combined oils, however a definitive proof would require further testing (Chao *et al.*, 2008).

Hydroperoxides [**1**: *Z*-2-methyl-2-butyric acid-(2-hydroperoxy-2-methyl-3-butenyl) ester, **2**: *Z*-2-methyl-2-butyric acid-(3-hydroperoxy-2-methylidenebutyl) ester], isolated from the ethanolic extract of the Roman chamomile flowers, showed an antibacterial activity against *E. coli*, *P. aeruginosa* and *E. faecalis*. The MIC values of compound 1 were 256 µg/ml against *E. coli* and 512 µg/ml against *P. aeruginosa*. The MIC values of compound 2 were 512 and 128 µg/mL, respectively (Hänsel *et al.*, 1993).

Ethyl acetate extract of Roman chamomile leaf showed potent vapour and contact activity against *Trichophyton mentagrophytes* determined by a box vapour and agar diffusion assay, respectively. The composition of the extract was similar to that of the Roman chamomile volatile oil (Inouye *et al.*, 2006).

Aqueous extract of Roman chamomile leaf completely inhibited the growth of *Aspergillus candidus*, *A. niger*, *Penicillium* sp. and *Fusarium culmorum* in a concentration of 92 g/ml media (Magro *et al.*, 2006).

Cytostatic activity

Nobilin, 1,10-epoxynobilin, 3-dehydronobilin and hydroxyisonobilin, isolated from Roman chamomile flower, showed *in vitro* cytostatic activity against human HeLa (cervix carcinoma cell line) and KB (nasopharyngeal carcinoma) cell lines (Holub and Samek, 1977). ED_{50} for hydroxyisonobiline were 0.5 µg/mL (1.5×10^{-6} M) and 1.23 µg/mL (3.5×10^{-6} M) for HeLa and KB cell lines, respectively (Holub and Samek, 1977) (Samek *et al.*, 1977) (Grabarczyk *et al.*, 1977).

Antioxidant activity

The antioxidant activity of Roman chamomile essential oil, acetone oleoresins (AO = dried acetone extract of fresh Roman chamomile flowers, containing the essential oil) and deodorized acetone extract (DAE = dried acetone extract of Roman chamomile flowers, from which the volatile oil content was primarily removed by hydrodistillation) has been investigated with various methods, including β-carotene bleaching assay, rapeseed oil stabilizing assay (peroxide value, oxygen absorption and UV absorption of formed aldehydes and ketones), measurement of free radical scavenging activity with different radicals ($DPPH^{\bullet}$, $ABTS^{\bullet+}$ and $^{\bullet}OH$), assessment of the influence on the enzyme xanthine oxidase, reducing power measured on Fe^{3+} and Fe^{2+} chelating effect (Piccaglia *et al.*, 1993) (Bandoniene *et al.*, 2000) (Povilaityte and Venskutonis, 2000) (Venskutonis *et al.*, 2005) (Podsedek *et al.*, 2009).

Roman chamomile oil had a high antioxidant activity in the β-carotene bleaching assay (Piccaglia *et al.*, 1993) showed significant inhibitory effect against hydroxyl radicals and acted as a ferrous ion chelator (Podsedek *et al.*, 2009).

Roman chamomile flower AO significantly inhibited the xanthine oxidase enzyme but showed no significant free radical scavenging activity in the $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ assays or reducing power converting Fe^{3+} to Fe^{2+} (Venskutonis *et al.*, 2005). Moreover, Roman chamomile flower DAE and AO significantly stabilized rapeseed oil during storing, measured by all three methods in a concentration of 0.1% w/w (Bandoniene *et al.*, 2000) (Povilaityte and Venskutonis, 2000).

Insecticidal activity

Roman chamomile volatile oil showed a high activity against the whitefly (*Trialeurodes vaporariorum*) nymphs at 0.0047 and 0.0093 µg/ml air using an impregnated filter paper test, whereas it was ineffective against the adult or egg forms. The results indicated that the mode of delivery of these oils was largely a result of action in the vapour phase, they might be toxic through penetration via the respiratory system (Choi *et al.*, 2004).

Antiplatelet activity

Roman chamomile oil dose dependently inhibited *in vitro* the induced platelet aggregation in guinea pig plasma, although with a modest potency. The oil showed no effect on clot retraction (Tognolini *et al.*, 2006).

Mobility decreasing effect

Effect of subcutaneously (350, 1250 and 2500 mg/kg) and i.p. (175 and 350 mg/kg) administered Roman chamomile oil was measured in male Wistar rats. The essential oil of Roman chamomile decreased the mobility of male Wistar rats by 51-76% compared to untreated control. The effect lasted for 50 min (Melegari *et al.*, 1988). Due to the high dosage, the results cannot be interpreted (Hänsel *et al.*, 1993).

Diuretic effect

Effect of subcutaneously (350, 1250 and 2500 mg/kg) and i.p. (175 and 350 mg/kg) administered Roman chamomile oil was measured in male Wistar rats. The oil caused a reduction in diuresis by 50% at 350 mg/kg or lower doses, whereas at higher doses an opposite effect was observed (Melegari *et al.*, 1988). Due to the high dosage, the results cannot be interpreted (Hänsel *et al.*, 1993).

Repeated oral administration of Roman chamomile flower aqueous extract (140 mg/kg, for 20 days) produced significant increase in urinary output and electrolyte (Na^+, K^+, Cl^-) excretion from the 8th day to the end of the treatment in spontaneously hypertensive rats (Zeggwagh *et al.*, 2009).

Hypotensive effect

Single oral administration of Roman chamomile aqueous extract (140 mg/kg) produced a slight but significant reduction in systolic blood pressure in spontaneously hypertensive rats after 24 hours of the administration. Daily oral administration of the extract in the same dose for 3 weeks produced a significant reduction in baseline arterial blood pressure starting from day 8 without affecting the heart rate. In both the single and repeated oral administration of Roman chamomile aqueous extract, the underlying hypotensive mechanism seems to be independent from plasmatic angiotensin convertase enzyme activity. However, the effect of single oral administration of Roman chamomile extract seemed to be independent of diuresis, whereas, in case of the repeated extract administration, the decrease in the blood pressure may be due to an increased water and electrolyte (sodium, potassium and chloride) excretion (Zeggwagh *et al.*, 2009).

Hypoglycaemic effect

Chamaemeloside, an apigenin glycoside containing a hydroxymethylglutaric acid (HMG) moiety, had no effect on glucose uptake in culture L6 muscle cells, but decreased the glucose plasma levels of Swiss-Webster mice by 19.2% and 31.9% at dosages of 125 and 250 mg/kg, respectively. Chamaemeloside exerted its effect 4 hours after i.p. administration. Chamaemeloside was also administered orally to normal mice to assess its effect on interprandial glycaemia and oral glucose tolerance. Although the interprandial glycaemia was not affected, chamaemeloside significantly improved glucose tolerance 4 hours after administration. Chamaemeloside might influence glucose homeostasis via multiple mechanisms but the results on cultured L6 cells might exclude the insulin-like activity. It is possible that HMG acid is being liberated from chamaemeloside and the observed activity is modulated in a similar fashion to that proposed for HMG itself (Witherup *et al.*, 1995) (Konig *et al.*, 1998). It has to be noted that the concentration of chamaemeloside in the herbal substance is much too low (0.05-0.1%) to have any significant effect on plasma glucose concentrations in man at the currently recommended daily dose (6 g) (Konig *et al.*, 1998).

In a further study, the effect on blood glucose concentrations and basal insulin levels in normal and streptozotocin-induced diabetic rats (STZ) was examined, after a single dose and after daily oral administration for 15 days of an aqueous extract of the aerial part of Roman chamomile at a dose of 20 mg/kg body weight. Single oral administration of Roman chamomile aqueous extract reduced blood glucose levels significantly 6 hours after administration in normal and STZ diabetic rats. Furthermore, blood glucose levels were decreased significantly in normal and STZ diabetic rats, after 15 days of treatment. Basal plasma insulin concentrations remain unchanged after treatment in both normal and STZ diabetic rats, so the mechanism seems to be independent of insulin secretion (Eddouks *et al.*, 2005).

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

Roman chamomile essential oil is relatively non-toxic following an acute exposure. Acute oral LD_{50} in rats was greater than 5 g/kg. Dermal application of 5 g/kg to rabbits did not result in any deaths. Undiluted Roman chamomile oil applied to the backs of hairless mice produced no irritating effects. When applied full strength to intact or abraded rabbit skin for 24 hours under occlusion, Roman chamomile oil was only mildly irritating. Animal studies have indicated the oil to be either mildly or non-irritant, and to lack any phototoxic effects (Opdyke, 1974).

There are no data available on the reproductive toxicity, genotoxicity and carcinogenicity of Roman chamomile.

3.4. Overall conclusions on non-clinical data

Limited pharmacological data are available for Roman chamomile, mainly on the antibacterial and antioxidant effect of the essential oil. The limited amount of toxicity data for Roman chamomile requires further investigation (Barnes *et al.*, 2002).

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 relevant data available.

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

No relevant data available.

4.2. Clinical Efficacy

See below.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Curative and preventive effects of externally applied emulsions containing alcoholic extract of Roman chamomile, alcoholic extract of German chamomile or steroid were examined in a placebo controlled trial in 20 volunteers. The chamomile extracts were included in model oil/water emulsions at a concentration of 5%. Preventive effectiveness was ascertained by using a sun stimulator to determine the threshold erythema time of skin areas which had regularly been treated with the test emulsion containing 0.15% triamcinolone acetonide or placebo. 15-20 min before the radiation the same skin part had been treated with one of the emulsions or placebo. As a control, a commercial product (COLIPA Low-Standard, SPF 4.0-4.4) has been used. Curative effectiveness was ascertained by comparing the subsidence of UV-induced erythemas on skin areas after 16-24 hours, which have been

treated with test emulsion containing 0.15% triamcinolone acetonide or placebo for 2 weeks. Whereas no preventive effect of the chamomile containing emulsions was found, the chamomile extract containing emulsions showed significant effectiveness to enhance the regeneration of skin erythemas compared to placebo. In particular, Roman chamomile led to a faster soothing of skin that has been irritated with by UV irradiation (Schrader *et al.*, 1997).

Assessor's comment:

There is no data in the publication on the criteria and mode of group formation, statistics used and about the fact, whether the trial was blinded or not.

A randomized, uncontrolled study was performed to assess the effects of massage and aromatherapy massage on cancer patients in a palliative care setting. One hundred and three patients were randomly allocated to receive massage using carrier oil (massage) and carrier oil plus Roman chamomile essential oil (aromatherapy massage). Outcome measurements included the Rotterdam Symptom Checklist (RSCL), the State-Trait Anxiety Inventory (STAI) and a semi-structured questionnaire, completed 2 weeks post-massage. There was a statistically significant reduction in anxiety in each massage group on the STAI. Scores improved significantly on RSCL including the psychological, quality of life, severe physical and severe psychological subscales for the aromatherapy massage group, whereas the improvement in the massage group did not reach the level of statistical significance. It was concluded that massage with or without essential oils appeared to reduce levels of anxiety. The addition of Roman chamomile essential oil seemed to enhance the effect of massage and to improve physical and psychological symptoms, as well as quality of life (Wilkinson *et al.*, 1999).

Assessor's comment:

The results of this study may not be easily generalised because the sample size was small, no entrance criteria was provided (so patients entered the study at various anxiety levels) and there was no control group.

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

No relevant data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

Clinical research assessing the effects of Roman chamomile is very limited and rigorous randomised controlled clinical trials are required. Clinical efficacy is not documented according to current scientific requirements (lack of substantiation for claimed uses was already reported by Blumenthal *et al.*, 1998); therefore a monograph on well-established use is not proposed.

Considering their similar chemical compositions, many of the activities described for German chamomile (*Matricaria recutita* L.) are thought to be applicable to Roman chamomile (Barnes *et al.*, 2002) and together with evidence of long-standing use, data support the traditional uses of Chamomillae romanae flos.

5. Clinical Safety/Pharmacovigilance

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

No relevant data were reported.

5.2. Patient exposure

Two clinical trials evaluated in the assessment report comprised altogether 123 patients (Schrader *et al.*, 1997) (Wilkinson *et al.*, 1999).

5.3. Adverse events and serious adverse events and deaths

Two cases of contact-allergic nipple eczemas in breastfeeding women were reported from England: both women had applied Kamillosan® ointment (suppliers Norgine Limited), product commercialized in the UK which contains extracts and oil of Roman chamomile (and not German chamomile); both patients had a strong positive reaction to chamomile oil 0.1% and negative reactions to other ingredients (McGeorge and Steele, 1991). However, it is questionable whether the product mentioned in the article contains Roman chamomile.

Sensitisation from compresses containing Roman chamomile has been reported in two patients from Belgium and Portugal who had a positive response to the 'sesquiterpene lactone mix' test, whereas a French patient sensitised from both compresses of Roman chamomile and a homoeopathic preparation containing Roman chamomile oil was negative to sesquiterpene lactone mix (Pereira *et al.*, 1997) (Giordano-Labadie *et al.*, 2000) (Bossuyt and Dooms-Goossens, 1994). Presumably, cases of sensitization are primarily caused by sesquiterpene lactones, but prolonged or repeated topical application seems necessary to reach levels at which sensitisation might be observed with tea consumption because of its lower content of allergens (Pereira *et al.*, 1997). Three of the five patients reported above had weak positive reactions to fragrance allergens and two to balsam of Peru (*Myroxylon pereirae*), which may reflect on potential for cross-reactions with sesquiterpenes (Bossuyt and Dooms-Goossens, 1994) (Giordano-Labadie *et al.*, 2000) (McGeorge and Steele, 1991). However, the connection between Roman chamomile oil hypersensitivity and Peru balsam and fragrance allergen allergy is hypothetic, according to Paulsen (Paulsen, 2002).

Idiosyncratic allergic reaction (head rush, tachycardia and nausea) has been reported in case of a nursing student after inhaling Roman chamomile volatile oil dropped on a strip in an aromatherapy class exercise. During the 10-year lecturer practice of the author, this was the only case of allergic reaction to Roman chamomile oil (Maddocks-Jennings, 2004).

Roman chamomile oil has been reported to be non-irritant to human skin (Opdyke, 1974).

No photosensitising effect of the coumarin compounds isolated from Roman chamomile has been observed (Barnes *et al.*, 2002).

Assessor's comment:

Since the causality of some case reports is doubtful and the reports are not related to herbal preparations or routes of administration as proposed in the monograph, these adverse events are not included in the monograph.

5.4. Laboratory findings

No data reported.

5.5. Safety in special populations and situations

Pregnancy

There have been no formal studies on the effects of Roman chamomile on pregnant women. In a systematic review on potential value of plant sources of antifertility agents, Farnsworth presents

folkloric data from papers published in the early 1960's. One of the cited sources mentions the abortive effect of the plant (plant part not defined). Two other references report an emmenagogue effect of the volatile oil or the whole plant. No further details are mentioned regarding the dosage (Farnsworth *et al.*, 1975). However, due to its theoretical properties as an abortifacient and emmenagogue, most experts agree that excess ingestion of Roman chamomile should be avoided during pregnancy. Roman chamomile has a class 2b safety rating from the American Herbal Products Association, advising not to use the plant during pregnancy, because of its potential abortifacient effects when taken at high doses due to its action on uterine smooth muscle and tendency to induce menstruation (Abramson *et al.*, 2010).

There are no reliable data from human studies or case reports on the emmenagogue and abortive effect of Roman chamomile. Safety during pregnancy has not been established. In the absence of sufficient data, the use during pregnancy is not recommended.

Lactation

No data available. Safety during lactation has not been established. In the absence of sufficient data, the use during lactation is not recommended.

Effect on fertility

No data available.

Drug interactions

The potential for preparations of Roman chamomile to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered (particularly where oral preparations of Roman chamomile are used). Coumarin compounds detected so far in Roman chamomile do not possess the minimum structural requirements (a C-4 hydroxyl substituent and a C-3 non-polar carbon substituent) for anticoagulant activity (Barnes *et al.*, 2007).

Since no clinically relevant interactions have been reported, none is included in the monograph.

Contraindications

In view of the documented allergic reactions and cross-sensitivities, Roman chamomile should be avoided by individuals with a known hypersensitivity to any members of the *Asteraceae* family (Barnes *et al.*, 2007). In addition, Roman chamomile may precipitate an allergic reaction or exacerbate existing symptoms in susceptible individuals (e.g. asthmatics) (Paulsen, 2002).

5.6. Overall conclusions on clinical safety

No health hazards or side effects are known in conjunction with the proper administration of Roman chamomile flower preparations at specified therapeutic dosages. The herbal substance possesses a small potential for sensitisation and use in individuals with a known hypersensitivity to the active substance and to other plants of the Asteraceae family is contraindicated.

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

6. Overall conclusions

The use of *C. nobile* has a long tradition in Europe. The provided clinical and non-clinical data do not fulfil the requirements of a well-established medicinal use with recognised efficacy and an acceptable level of safety of Roman chamomile products.

On the basis of the long medicinal tradition in the specified conditions, Roman chamomile products can be registered as traditional herbal medicinal products for the symptomatic treatment of mild, spasmodic gastro-intestinal complaints.

Toxicological data on Roman chamomile is very limited. Nonetheless, neither the chemical composition nor the long-term widespread use in the European Union suggest that there is a risk associated with the use of Roman chamomile products when administered at the specified posology and strength. Due to the lack of data on acute and chronic toxicity, repeated dose toxicity, genotoxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, the safety of the therapeutic use of *C. nobile* flower and its preparations is mostly derived from long-standing use and experience.

The herbal substance possesses a small potential for sensitisation. In view of the documented allergic reactions and cross-sensitivities, Roman chamomile is contraindicated in individuals with a known hypersensitivity to the herbal substance and to other plants of the Asteraceae family.

Considering the long-standing traditional use of Roman chamomile flower in Europe and the fact that the chemical composition, indications and uses of the Roman and German chamomile are similar (Barnes *et al.*, 2002) (Hänsel *et al.*, 1993) (Bisset, 1994), the benefit/risk balance of the medicinal use is positive (reference is made to quality requirements of the pharmaceutical legislation).

The lack of relevant data (reproductive toxicity, genotoxicity and carcinogenicity) does not allow the establishment of a Community list entry.

Annex

List of references