EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

# Assessment report on *Marrubium vulgare* L., herba

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) | *Marrubium vulgare* L., herba |
| Herbal preparation(s) | a) Comminuted herbal substance<br>b) Powdered herbal substance<br>c) Expressed juice (DER 1:0.70-0.90)<br>d) Liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 20-30% V/V |
| Pharmaceutical form(s) | Comminuted herbal substance as herbal tea for oral use.<br><br>Herbal preparations in solid or liquid dosage forms for oral use. |
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# 1. Introduction

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

- Herbal substance(s)

*Marrubium vulgare* L., herba

**Definition of the herbal substance**

Diverse national monographs for White Horehound have been replaced by the monograph published in the European Pharmacopoeia 5th ed. 2005 (5.1) and the current European Pharmacopoeia 7th edition 2011 (7.0) (01/2008:1835 corrected 6.0) White Horehound - Marrubii herba. The definition of Marrubii herba is "Whole or fragmented dried flowering aerial plants of *Marrubium vulgare* L. Content: minimum 0.7% marrubiin ($C_{20}H_{20}O_4$; M: 332.4) (dried drug)." Characters: bitter taste.

Material of commerce is usually supplied in the cut or crushed form. It is obtained mainly from European countries and North-west Africa. The herbal substance has a pleasant odour and a bitter, aromatic taste. (BHP, 1990).

**Name**

The species *Marrubium vulgare* L., Lamiaceae is known under the synonyms: *Marrubium album* GILB., *Marrubium germanicum* SCHRANK, *Marrubium lanatum* KUNTH, and *Prasium marrubium* E.H.L. Krause; it is described as herba Marrubii, herba Marrubii albi, herba Marrubii vulgaris and herba prasii (Blaschek *et al*., 2006).

In European countries, *Marrubium vulgare* is known by the following common names: German: Weißes Andornkraut, Gemeiner Andorn, Mauer-Andorn, Weißer Dorant; English: Common Horehound, hoarhound, houndsbene, marvel, White Horehound; French: Herbe vierge, marrube, Marrube blanc; Italian: Erba apiola, marrobio, mentastro; Spanish: Marrubio (Blaschek *et al*., 2006).

**Adulteration and confusion**

Confusion with *Ballota nigra* L., *Nepeta cataria* L., *Stachy germanicus* L., *Marrubium incantum* DESR or *Marrubium remotum* KIT is possible (Blaschek *et al*., 2006).

Berger (1954) reports that, on the market, Marrubii nigri herba is also a traditionally used herbal substance, which consists of the herb of *Marrubium peregrinum* L.

The current Natural Health Products Ingredients Database of Health Canada contains a monograph "Black Horehound" (Health Canada, 2008).

Nagy & Svajdlenka (1998) determined the chemical composition of the essential oils obtained from the flowering aerial parts of *M. vulgare* L. and *M. peregrinum* L. There were some similarities in chemical composition between both oil samples, but the amounts of corresponding components were quite different. Most of determined constituents were sesquiterpenes. Some specific substances were present in both oils up to 20% of content. It was concluded that the composition difference may cause an important change in the biological activities of both oils.

The HMPC monograph concerns only *Marrubium vulgare* L.

**Principal constituents of the herbal substance**

According to Blaschek *et al*. (2006) the principal constituents of the herbal substance are:

- traces of essential oil (0.05-0.06%) with monoterpenes such as camphene, p-cymol, fenchene, lomonene, α-pinene, sabinene, and α-terpinolene
- diterpenes of labdane-type with marrubiin (0.12-1%) and its precursor pre-marrubiin (0.13%), marrubenol, a labdane-hemiacetale, marrubiol, peregrinol and vulgarol
- tannins (up to 7%) and hydroxylcynamic acid-derivates, e. g. acteoside, chorogenic acid, caffeic acid, 1-caffeoylquinic acid and cryptochlorogenic acid, but no rosmarinic acid. Acteoside is used as qualitative marker.
- flavonoids: flavone and flavonol glycosides and their respective aglycones (e.g. apigenin, luteolin, quercetin, chrysoeriol, vicenin II, vitexin) lactoylflavones, luteolin-7-lactate, apigenin-7-lactate
- nitrogen-containing compounds: 0.2% choline and 0.3% betonicine
- minerals, in particular potassium salts

For the bitter taste the furanic labdane dipertene marrubiin is responsible. Up to 4 mg of furanic labdane deterpenes *per* g fresh weight were found, most in young leaves and buds. Depending on the vegetation period or the extracting conditions, the extracts contain marrubiin, pre-marrubenol or marrubenolacetat (Knöss & Zapp, 1998; Knöss, 2006). According to the European Pharmacopoeia 7$^{th}$ edition 2011, the marrubiin content of the crude drug should be at least 0.7%.

**Herbal preparation(s)**

**Information about products on the market in the Member States**

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following herbal substances have been on the European market:

Herbal preparations which have been reported to be marketed under well-established use:

- expressed juice from fresh Marrubii herba (1:0.70-0.90)

| Member State | Medicinal Product (Mono Preparation) | Regulatory Status |
|---|---|---|
| Germany | expressed juice from fresh Marrubii herba (DER 1:0.70-0.90)<br>posology: 3 times daily 10-20 ml | since 1976 MA |

Herbal preparations which have been reported to be marketed under traditional use:

- liquid extract from Marrubii herba (DER 1:0.9-1.1), extraction solvent: ethanol 30% V/V
- powdered herbal substance

| Member State | Medicinal Product (Mono Preparation) | Regulatory Status |
|---|---|---|
| Germany | liquid extract from Marrubii herba (DER 1:0.9-1.1), extraction solvent ethanol 30% (V/V)<br>posology: 3 times daily 1.5-2 ml | since 1976 TU |
| Spain | capsules containing 225 mg of powdered herbal substance | since 1992 TU |

| | | |
|---|---|---|
| | posology: 3 times daily 1-2 capsules | |

**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.**

According to the overview of the marketed products, in Austria and Hungary, Marrubii herba is used in combination with other herbal substances/herbal preparations. No detailed information about the combination substances and indications is available.

In the Czech Republic, combination preparations and tea preparations of *Marrubium vulgare* are on the market. They are used as adjuvant therapy in mild gastrointestinal disorders, loss of appetite and mild functional biliary tract disorders. The main combination substances are Menthae piperitae herba, Rhei radix, Agrimoniae herba, Boldi folium, Taraxaci radix cum herba, Frangulae cortex, Matricariae flos, Menthae piperitae herba, Absinthii herba, Gentianae radix, Angelicae radix, Calami radix, Tormentillae radix, Myrrha, Zedoariae radix, Myristicae semen, Macis, Juglandis fructus cortex, Theriak sine opium (Angelicae radix, Valerianae radix, Cinnamomi cortex, Zedoariae radix, Cardamomi fructus, Myrrha).

In Denmark, there has only been one combination product with Marrubii herba on the market (licensed in January 1997 and withdrawn in June 1999). It was used against coughing and catarrh in upper respiratory passages for short periods. The combination substances were Liquiritiae radix, Thymi herba, Hederae helicis folium and Pimpinellae radix.

In Poland, the herbal substance is only available in 2 combination products. The average number of combination substances is 3 to 5. In one product, the combination substances are Menthae piperitae folium, Matricariae flos, Frangulae cortex and Rhei radix. It is used in the indication for mild digestive complaints (feeling of fullness, meteorism) and in lack of appetite. Another product contains an extractum compositum fluidum (1:2), extraction solvent: water, of Millefolii herba, Marrubii herba, Melissae folium, Foeniculi fructus (3/2/3/2). It is used in children in lack of appetite.

In Slovak Republic, the herbal substance is only available in combination products. The average number of combination substances is 3 to 5. The main combination substances are Agrimoniae herba, Inulae radix, Rhei radix and Rubi idaei folium. It is used in the indication biliary disorders, as mild laxans and for reduction of meteorism and cramps.

**Non-medicinal uses**

Extracts of *M. vulgare* herba are also used for flavouring beverages and candies (Vincenzi, 1995). In the USA it is generally recognized as safe (CFR, 2012) and the Council of Europe permitted Marrubii herba as flavouring category N2 (Bradley, 1992).

This assessment report supports the Community herbal monograph, which refers exclusively to Marrubii herba as a single active substance. With respect to the overall evaluation of the existing data on efficacy, the monograph addresses only the traditional use.

## Regulatory status overview

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| Austria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☒ Other Specify: | tea-combinations only |
| Belgium | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Bulgaria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| Croatia | | | | | food supplements only |
| Cyprus | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Czech Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination prod. only |
| Denmark | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination prod. only |
| Estonia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| Finland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| France | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Germany | ☒ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | since 1976 |
| Greece | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| Hungary | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination prod. only |
| Iceland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Ireland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Italy | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Latvia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| 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: | |
| The Netherlands (Malrove) | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☒ Other Specify: | homeopathic medicinal prod.; food supplements |
| Norway | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| Poland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination prod. only |
| Portugal | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Romania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Slovak Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination prod. only |
| Slovenia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| Spain | ☐ MA | ☒ TRAD | ☐ Other TRAD | ☐ Other Specify: | since 1992 |
| Sweden | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | no prod. on the market |
| 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.

### 1.2. Search and assessment methodology

A literature search was performed in April 2012 using the common databases of the DIMDI database information system (e.g. MEDLINE, EMBASE, SciSearch, Cochrane Library). The search term was "marrubium". The literature list of 280 articles was examined. Additional hand searches were performed in books on herbal medicines and plant monographs in the BfArM own library. The bibliographies of included trials and other relevant reviews were searched to identify further potential trials.
In the list of references, the references supporting the assessment report are listed first and secondly references used but not introduced into the assessment report.

# 2. Historical data on medicinal use

### 2.1. Information on period of medicinal use in the Community

Marrubii herba is included in pharmacopoeias and standard text books of phytotherapy since many decades. Benedum *et al*. (2006) describes old references on medicinal use of Marrubii herba such as Dioskurides ("… it is given to patients suffering from … cough … also purges away the mucus from the chest", Hildegard von Bingen ("… against cough"), Matthiolus ("… helps against cough …") and Tabernaemontanus ("… purifies chest and lungs from coarse mucus…"). Gilg *et al.* (1927) describe Marrubii herba for the use in pulmonary diseases. Madaus (1938) notes that Marrubii herba is mentioned since Paracelsus as "preparation for the lung" and from Lonicerus as "emenagogum, expectorans and diureticum". In the old phytotherapeutic book of Dragendorff (1898), 'herba Marrubii' is listed for medical use in catarrhs. 'Herba Marrubii albi' is also noted as phytotherapeutic drug in Merck´s Index of 1910. The old textbook 'Potter's Cyclopaedia of Botanical Drugs and Preparations' (1941) describes Horehound as: "Bitter tonic, expectorant and diuretic. Is perhaps the most popular of herbal pectoral remedies. It is exceedingly valuable in coughs, colds, and pulmonary affections. It has a pleasant taste and makes a nice tonic. In many parts it is brewed and sold as Horehound Ale, making an appetising and healthful beverage". The old Belgian literature "Materia Medica Vegetabilis" (Steinmetz, 1954) describes the use as follow: "White Horehound herb is indicated for the use in form of a decoction boiled into a thin syrup, with honey against coughs, hoarseness of long standing and bronchitis. It is expectorant, diuretic, carminative and stimulant. It is also used against diarrhoea, piles and jaundice".

In the German-speaking areas, Marrubii herba is traditionally used especially in context of a bitter remedy and, in the Anglo-American and in the Mediterranean language areas, in context of respiratory disorders (Knöss, 2006). According to the PDR for herbal medicines (1998), folk uses of *Marrubium vulgare* are internally for acute and chronic bronchitis, whooping cough, asthma, tuberculosis, pulmonary catarrh, respiratory infections, diarrhoea, jaundice, debility, painful menstruation, and as a laxative in higher doses; externally for skin damage, ulcers and wounds.

Literature reports suggest that *Marrubium vulgare*, herba is traditionally used also in a number of countries outside of Europe. Haq *et al*. (2010) describe the use for cough, catarrh, emetic, hysteria, rheumatism in Pakistan. De Souza *et al*. (1998), de Oliveira *et al*. (2011) and Meyre-Silva *et al*. (2005) report on the traditional use to treat inflammation, gastrointestinal disorders and respiratory diseases in Brazil. In Tunisian folk medicine, Horehound was used as hypotensive, hypoglycaemic and cardiotonic (Kadri *et al*., 2011). Pages et Comte (1927) describe the traditional use of Horehound as antiarrythmic in France. Kanyonga *et al*. (2011) report a frequent use in folk medicine in the Mediterranean North Africa (Morocco).

The following list shows examples of pharmacopoeias and standard text books with monographs of White Horehound.

- British Herbal Compendium (Bradley 1992)
- Martindale, The Extra Pharmacopoeia 1967
- British Herbal Pharmacopoeia (BHP) 1976, 1983, 1990, 1996
- British Pharmaceutical Codex 1934
- Österreichisches Arzneibuch (ÖAB) – Pharmacopoeia Austriaca 1960, 1981, 1990
- Pharmacopée Française 1989
- DAC 1995, 1997, 2003
- Kommission E (German Commission E) 1990
- Blaschek *et al*. 2006
- Berger 1954
- Pahlow 1979

Based on pharmacopoeias and standard text books of phytotherapy for Marrubii herba, the requirement for a period of at least 30 years of medicinal use, from Directive 2004/24/EC, for qualification as a traditional herbal medicinal product, is fulfilled.

According to the information provided by the National Competent Authorities in the overview of the marketed products, qualification as a traditional herbal medicinal product is fulfilled for:

- Expressed juice (DER 1:0.70-0.90): 10-20 ml, 3 times daily
- Liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 30% (V/V): 1.5-2 ml, 3 times daily

For the HMPC monograph, additionally preparations with a 30-year traditional use based on pharmacopoeias (BHP, 1983; Bradley, 1992) are recommended:

- Herbal substance for tea preparation: 1-2 g, 3 times daily
- Liquid extract (DER 1:1), extraction solvent ethanol 20% (V/V): 2-4 ml, 3 times daily

The two preparations liquid extract [(DER 1:0.9-1.1), extraction solvent ethanol 30% (V/V)] and liquid extract [(DER 1:1), extraction solvent ethanol 20% (V/V)] are combined into:

- liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 20-30% (V/V): 1.5-4 ml, 3 times daily.

The powdered herbal substance for oral use in solid dosage forms could also be integrated into the monograph. Tradition is based on the reference given in BHP (herbal substance: 1-2 g 3 times daily, at least since 1983), posology was adapted to a product on the market in Spain since 1992:

- Powdered herbal substance: 225-450 mg, 3 times daily

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

For the herbal substance and preparations thereof the following indications are described in pharmacopoeias and literature:

Respiratory and thoracic disorders:

| | |
|---|---|
| Catarrhs of the respiratory tract | Blaschek *et al*. (2006) |
| Acute bronchitis, non-productive coughs, catarrh of the respiratory tract | Bradley (1992) |
| (111) Traditionally used for the symptomatic treatment of coughs.<br>(113) Traditionally used in the course of acute benign bronchial affection. | Avis aux fabricants (1998) |
| Catarrhs of the respiratory tract | Blumenthal *et al*. (1998) |
| Traditionally used to support the secretolytic activity in the respiratory tract. | Indikationsliste (2005) |
| Acute or chronic bronchitis. Bronchitis with non-productive cough. Whooping cough. | BHP (1976, 1983) |
| Expectorant | BHP (1976, 1983, 1990, 1996) |
| Horehound is expectorant. In the form of infusion, oxymel or syrup, it is a popular domestic remedy for coughs, colds, and pulmonary affections. | British Pharmaceutical Codex (1934) |
| Catarrhs of the respiratory tract | DAC (1995, 1997, 2003) |
| Cough/bronchitis; respiratory catarrh | PDR for Herbal Medicines (1998) |

Gastric disorders:

| | |
|---|---|
| Dyspeptic complaints such as bloatedness and flatulence. Marrubic acid works as a choleretic. | Blumenthal *et al*. (1998) |
| Traditionally used to support the gastro-intestinal function. | Indikationsliste (2005) |
| Dyspeptic complaints such as fullness and flatulence. | Blaschek *et al*. (2006) |
| Dyspepsia | Bradley (1992) |
| Laxative in large doses | British Pharmaceutical Codex (1934) |
| Dyspeptic complaints | DAC (1995, 1997, 2003) |
| Species cholagogues | ÖAB (1960, 1981, 1990) |
| Dyspeptic complaints, bloating and flatulence liver and gallbladder complaints | PDR for Herbal Medicines (1998) |

Further traditional indications:

| | |
|---|---|
| Loss of appetite | Blaschek *et al.* (2006); Blumenthal *et al*. (1998); DAC (1995, 1997, 2003); PDR for Herbal Medicines (1998) |
| Lack of appetite | Bradley (1992) |

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following indications are found:

- expressed juice from fresh Marrubii herba (1:0.70-0.90): catarrhs of the respiratory tract; dyspeptic complaints such as fullness and flatulence
- liquid extract from Marrubii herba (1:0.9-1.1), extraction solvent: ethanol 30% (V/V): traditionally used to support the secretolytic activity in the respiratory tract.

Based on literature and indications for marketed products, the following indications are accepted in the monograph:

a) Traditional herbal medicinal product used as an expectorant in cough associated with cold.

b) Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic complaints such as bloating and flatulence.

c) Traditional herbal medicinal product used in temporary loss of appetite.

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

Some of the references given in this chapter provide evidence for the 30-year medicinal use, while the more recent references are seen as supportive.

**Posology**

- Herbal substance for tea preparation (comminuted) or for oral use (powdered)

| **References** | **Dosage** | **Mode of Administration** |
|---|---|---|
| Blumenthal *et al*. (1998) | daily dose: 4.5 g of herbal substance | tea preparation for oral use |
| Bradley (1992) | unless otherwise prescribed, three times daily: dried herb, 1-2 g or in infusion | oral use |
| BHP (1976) | three times daily: dried herb, 1-2 g or by infusion | oral use |
| DAC (1995, 1997, 2003) | daily dose: 4.5 g of drug | oral use |
| EB 6 (1953) | dried herb: single dose 1.5 g in infusion | oral use as infusion |
| ÖAB (1960, 1981,1990) | dried herb: single dose 1.5 g in infusion | oral use as infusion |

| | | |
|---|---|---|
| PDR for herbal medicines (1998) | comminuted herb as infusion:<br>1-2 g herbal substance taken up to 3 times daily | |
| Wichtl (1984, 1997, 2002)<br>Schilcher & Kammerer (2000)<br>Schilcher *et al*. (2007) | comminuted herb as infusion:<br>single dose 1.5 g; daily dose: 4.5 g | as choleretic, the tea should be taken 30 min before meals<br>For the use as expectorant the tea should be taken several times a day. |
| For the monograph the following dosage is recommended:<br>herbal tea: 1-2 g of the comminuted herbal substance in 250 ml of boiling water as a herbal infusion 3 times daily | | |

– Expressed juice (DER 1:0.70-0.90)

| **References or MA** | **Dosage** | **Mode of Administration** |
|---|---|---|
| Marketing authorisation | in adults and adolescents over 12 years<br>3 times daily 10-20 ml | oral use |
| Blumenthal *et al*. (1998) | unless otherwise prescribed, daily dose:<br>2-6 tablespoonful of pressed juice or equivalent preparations | oral use |
| PDR for herbal medicines (1998) | pressed juice: daily dose 30-60 ml | |
| Wichtl (1984, 1997, 2002)<br>Schilcher & Kammerer (2000)<br>Schilcher *et al*. (2007) | pressed juice: daily dose: 2-6 tablespoons | |
| For the monograph the following dosage is recommended:<br>expressed juice (DER 1:0.70-0.90):<br>10-20 ml, 3 times daily | | |

– Liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 30% (V/V)

| **Marketing authorisation** | **Dosage** | **Mode of Administration** |
|---|---|---|
| Marketing authorisation | adults and adolescents over 12 years: 3 x daily 1.5-2 ml | oral use |
| For the monograph the following dosage was considered:<br>liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 30% (V/V):<br>1.5-2 ml, 3 times daily | | |

– Liquid extract (DER 1:1), extraction solvent ethanol 20% (V/V)

| References | Dosage | Mode of Administration |
|---|---|---|
| Bradley (1992) | unless otherwise prescribed, three times daily: 1-2 ml | oral use |
| BHP (1976, 1983) | three times daily:<br>2-4 ml | oral use |
| PDR for herbal medicines (1998) | 2-4 ml 3 times daily | |
| For the monograph the following dosage was considered:<br>liquid extract (DER 1:1), extraction solvent: ethanol 20% (V/V): 1-4 ml, 3 times daily | | |

The two preparations [liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 30% (V/V)] (from the market overview) and [liquid extract (DER 1:1), extraction solvent ethanol 20% (V/V)] (from references) are combined into a liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 20-30% (V/V).

For this combined preparation, the following dosage is recommended:

Liquid extract (DER 1:0.9-1.1), extraction solvent ethanol 20-30% (V/V): 1.5-4 ml, 3 times daily.

**Route of administration**

Oral use is the only route of administration for White Horehound herb preparations in the traditional indications discussed in this assessment report.

**Duration of use**

No information on the duration of use is available. In order to assure safe use as a traditional herbal medicinal product within the scope of the simplified traditional use registration scheme, the duration of use is limited in the context of each respective indication:

Indication 1): Traditional herbal medicinal product used as an expectorant in cough associated with cold: “If the symptoms persist longer than 1 week, a doctor or a qualified health care practitioner should be consulted.”

Indications 2) and 3): Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic complaints such as bloating and flatulence; Traditional herbal medicinal product used in temporary loss of appetite: “If the symptoms persist longer than 2 weeks, a doctor or a qualified health care practitioner should be consulted.”

**Method of administration**

For the use in the indications 2) and 3), the herbal preparation should be taken ½ hour before the meals (Steinegger & Hänsel, 1968; Hänsel & Haas, 1984; Wichtl, 1984; Wichtl, 2002; Neubeck, 2012).

# 3. Non-Clinical Data

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

**Primary pharmacodynamics**

**Herbal preparations**

Antispasmodic effects/anti-inflammatory effects/analgesic effects

Schlemper *et al*. (1996) evaluated the effects of a hydroalcoholic extract of the roots and aerial parts of *M. vulgare* (DER 1:3, 50% ethanol) in several smooth muscle preparations *in vitro* (guinea pig ileum, rat duodenum, rat uterus, rat stomach fundus). The results showed that the extract exerts a significant antispasmodic activity which inhibits the action of some neurotransmitters, such as acetylcholine, bradykinin, prostaglandine E2, histamine and oxytocin. The findings suggest a non-competitive inhibitory profile with concentration-dependent inhibition (100, 300 and 1,000 µg/ml) and a decrease of maximal response according to the case of the interference in any intracellular event by agonists.

De Souza *et al*. (1998) investigated the possible analgesic effects of a hydroalcoholic extract obtained from *M. vulgare* in different models of pain in mice. Air dried leaves, stems and roots of *M. vulgare* were minced and extracted with 50% ethanol-water (DER 1:3), being macerated at room temperature for 14 days. The results show significant and dose-dependent analgesic effect of the hydroalcoholic extract given intraperitoneally (i.p.) 30 min or per os (p.o.) 60 min beforehand, being effective in inhibiting acid-induced writhing response in mice. It exhibited analgesic potency with $ID_{50}$ values at 22.2 mg/kg for the i.p. and 272.2 mg/kg for the p.o. routes. At 60 mg/kg i.p. and 600 mg/kg p.o. the extract practically abolished the irritant-induced pain of the test, characterized by writhing responses. In the formalin test, the extract significantly inhibited in a dose-dependent manner both the first and the second phases with mean potencies ($ID_{50}$) of 280 mg/kg p.o. and 30 mg/kg i.p. The formalin-induced oedema was inhibited in a dose-dependent manner by i.p. (maximal inhibition of 62.9±3%) but not by p.o. administration. In the hot-plate test, the extract did not increase the latency period of pain induced by the thermal stimuli.

Kanyonga *et al*. (2011) described the effects of a methanolic extract of *M. vulgare* (200 g powder of the plant was extracted in a Soxhlet apparatus with methanol). The extract was evaporated to dryness to give a yield of 39.2% (DER ~2.5:1). The extract (200 mg/kg, oral) significantly inhibited (35.3%) abdominal constriction in mice in p-benzoquinone-induced abdominal constriction test. Furthermore, the extract showed a significant inhibition (34%) at a dose of 200 mg/kg in the carrageenan-induced hind paw oedema test, close to that of indomethacin (38.7%). No inhibition was observed at 100 mg/kg dose. In the hind paw oedema induced by prostaglandin E2, the extract at the 200 mg/kg dose showed considerable inhibition (23.2-27.2%) while the 100 mg/kg extract did not demonstrate any noticeable activity. Maximum inhibition was observed after 45 min.

Gastroprotective activity

De Oliveira *et al*. (2011) assessed the gastroprotective properties of the methanol extract (1.5 kg plant material was macerated 7 days with 4 l methanol) and marrubiin obtained from the leaves of *M. vulgare*. In the model of ethanol-induced ulcers in Swiss mice, they observed a significant reduction in all the parameters analysed (lesion index, the total injured area and the percentage injured area). The curative ratios obtained were 49.31±0.57, 74.31±0.91, and 79.86±0.59 for the groups treated with 50 and 100 mg extract/kg and omeprazole (30 mg/kg, oral), respectively. In the indomethacin-induced ulcers, the percentages of ulcer inhibition were 50.32±5.6, 66.24±4.3, 82.17±04.09 and 67.52±4.38, for the groups treated with 25, 50 and 100 mg extract/kg and positive control cimetidine.

In both models, marrubiin (25 mg/kg) produced a significant reduction in all the parameters when compared with the control group. There was also a significant increase in pH (*M. vulgare* extract at doses of 50 and 100 mg/kg, marrubiin at a dose of 25 mg/kg) and mucus production in the groups treated with *M. vulgare* extract and marrubiin. These results were seen as indicator that the extract has cytoprotective activity that is correlated, at least in part, with the presence of marrubiin. The data suggest that the gastroprotective effect induced by the *M. vulgare* extract is slightly related to SHs. On the other hand, the gastroprotection mediated by marrubiin seems to be much more closely related to SHs.
The authors point out that the combination of the anti-inflammatory, antinociceptive and gastroprotective effects in the same plant extract or compound should be taken into account because of the limitation of analgesic agents that produce gastric irritation, bleeding and mucosal cellular damage.

*Assessor´s comment*
*Only a few studies can be brought in connection with primary pharmacodynamic effects of M. vulgare. They are not conducted with aqueous extracts nor with ethanolic extracts prepared with ethanol in the strength proposed by the monograph; however even the results with methanolic extracts or with ethanolic extracts (ethanol 50%) can be seen at least as adding some plausibility.*
*An antispasmodic effect of a hydroalcoholic extract of the roots and aerial parts of Marrubium vulgare was shown by Schlemper et al. (1996) in several smooth muscle preparations in vitro, even though a direct correlation between in vitro and in vivo is not possible. Analgesic effects were shown for a hydroalcoholic extract (DER 1:3) in acid-induced writhing response in mice. It exhibited analgesic potency with $ID_{50}$ values at 272.2 mg/kg for the oral route, being equivalent with a human equivalent dose (HED) of 22 mg/kg. This corresponds to a human dose of 1.32 g extract (22 mg x 60 kg) = 0.44 g herbal substance. Therefore the effects seen can be interpreted as plausible although some uncertainty about the extract used exists.*
*The effects of the methanolic extracts seem, at least in terms of the concentration, plausible to be relevant for the aqueous and ethanolic preparations of the monograph.*
*Gastroprotectice activities were recognised for the methanolic extract while the role of marrubiin has to be discussed, because according to the Ph. Eur. the amount of marrubiin is up to ~1% while the results by De Oliviera et al. were achieved with half the concentration of the extract (would be equivalent of 50%). The dosage of 200 mg/kg oral in mice for the antispasmodic and anti-inflammatory effects equals a HED of 16 mg/kg. For a 60 kg adult, this would mean a single dose of ~1 g extract. According to the yield of extraction, this equals an amount of 2.5 g herbal substance. Even though the interpretation of the results for clinical relevance is limited, at least in the animal testing, the dosage equals the traditional human doses.*

**Isolated compounds**

Choleretic activity
Krejci & Zadina (1959) investigated the stimulating effects on bile secretion of marrubiin, marrubiinic acid and its sodium salt in rats. The bile was collected in the duodenum together with the pancreatic juice. Marrubiin failed to stimulate choleresis, while secretion was materially enhanced by marrubiinic acid at doses of 2-3 mg/100 g rat and its sodium salt.

Anti-inflammatory effects
Sahpaz *et al*. (2002) investigated the chemical composition of a polar extract of *M. vulgare* to justify the therapeutic uses. The phytochemical analysis of a polar extract led to the isolation of 5 phenylpropanoid esters: 1) caffeoyl-L-malic acid; 2) acteoside; 3) forsythoside B; 4) arenaiodside; 5) ballotetroside. Quantitatively, compounds 1-5 are present in almost equal amounts, of circa 0.5-1% of the dried flowered aerial parts. The authors tested the capacity of the 5 compounds to inhibit the

COX activity *in vitro* ($10^{-3}$, $10^{-4}$, $10^{-5}$ M). One unit of COX-1 from seminal vesicles and one of COX-2, from sheep placenta. Indomethacin, a non-selective COX inhibitor and nimesulide, a preferential COX-2 inhibitor were used as reference drugs. Compounds 2-4 showed the strongest COX-2 inhibition with activities ranging from 23.1 to 32.8% at a concentration of 1 mM and $IC_{50}$ varying from 0.49 to 0.69 mM in the range of that of nimesulide. These three compounds did not exhibit any significant inhibition (1.2-1.9%) on COX-1 at the same concentration.

Stulzer *et al*. (2006) analyzed marrubiin in a model of microvascular leakage in mice ears. The results obtained for $ID_{50}$ values (mg/kg, i.p.) and maximal inhibition (%), for the different phlogistic agents used, were: histamine 13.84 mg/kg and 73.7%; bradykinin 18.82 mg/kg and 70.0%; carrageenan 13.61 mg/kg and 63.0%. In addition, marrubiin (100 mg/kg i.p.) significantly inhibited the ovalbumin-induced allergic oedema in actively sensitised animals.

Analgesic effects

De Jesus *et al*. (2000) analysed the antinociceptive profile of marrubiin in different models of nociception in mice. The results showed that marrubiin exhibits dose-related antinociceptive effect and inhibited acetic acid-induced writhing responses in mice. The $ID_{50}$ value (i.p) was 2.2 µmol/kg in the writhing test. The effect was observed over a long time period, extending its action until 5 h after the analgesic stimuli with acetic acid. Marrubiin was more potent than some known analgesic drugs, as it had lower $IC_{50}$ compared with i.p. aspirin and i.p. diclofenac. When the animals were treated with naloxone (85 mg/kg, i.p.), a non-selective morphine receptor antagonist, no change was observed in the antinociceptive effect of marrubiin, so the authors concluded that marrubiin is effective in a non-opioid way. This was confirmed by the lack of antinociceptive effects in the hot-plate test (180 µmol/kg), a technique that has a selectivity for opioid-derived analgesics.
In the formalin test, marrubiin significantly inhibited dose-dependently the first phase, peaked after 5 min (representing the neurogenic pain) and after 15-30 min (second phases, representing the inflammatory pain) by i.p. and oral routes. The calculated $ID_{50}$ values for first and second phases were 6.6 (4.8-8.4) (first phase) and 6.3 (5.4-7.2) (second phase) µmol/kg for the i.p. route, with maximum inhibition of 78±5 and 83±4%, respectively. When analysed by the oral route, marrubiin presented $ID_{50}$ of 126 (109-135) and 108 (97-137) µmol/kg with maximum inhibition of 75±3 and 99±1% for first and second phases. When analysed in the capsaicin-induced neurogenic nociception, marrubiin promoted a significant and dose-dependent inhibition of chemical induced pain. The calculated $ID_{50}$ value was 28.8 (27.3-29.3) µmol/kg with maximum inhibition of 76±5%.

Meyre-Silva *et al*. (2005) obtained some marrubiin derivates (marrubiin, marrubiinic acid, marrubenol, marrubiinic acid benzyl ester, marrubiinic acid methyl ester). In the writhing test (at 10 mg/kg, i.p.) marrubiinic acid caused 80% inhibition of the abdominal constrictions and was submitted to further tests. Marrubiinic acid exhibited a similar analgesic profile to that of marrubiin in the experimental models (spinal and supraspinal antinociception when assessed against both formalin- and capsaicin-induced neurogenic pain as well as in glutamate-induced hyperalgesia in mice). Although marrubiinic acid showed lesser antinociceptive effects than its prototype marrubiin, it was more potent than some clinically used drugs such as acetylsalicylic acid or paracetamol.

*Assessor´s comment*

*In contrast to marrubiin, acid marrubiin failed to stimulate choleresis in rats after i.v. application. In in vivo experiments in rats choleretic activity of marrubiinic acid was shown. The pharmacokinetics of marrubiin into marrubiinic acid and the concentrations needed for the pharmacological effect is still not examined. Marrubiinic acid may contribute to the pharmacodynamic plausibility, but the clinical relevance is unclear. Furthermore the i.v. administration is not the clinically intended route of administration. Some results suggest that marrubiin interferes with some common mechanisms of phlogistic agents used, but until now it was not possible to determine where it is acting. For some phenylpropanoid esters extracted of M. vulgare and marrubiin, anti-inflammatory and analgesic effects*

*could be shown in vitro and in vivo, respectively. Results are mostly of low relevance, as they were conducted in vitro or with i.p. administration. Furthermore there is no knowledge about the plasma concentrations of those substances in the clinical situation.*

**Secondary pharmacodynamics**

**Herbal preparations**

Antimicrobial and anti-infective activity

Diaz *et al*. (1988) tested an aqueous extract (DER 1:10) and an ethanolic extract (no further information) of *M. vulgare* for antibacterial activity against *Bacillus subtilis*, *Micrococcus luteus* and *Escherichia coli* in disc diffusion method. Both extracts showed no activity.

Keleş *et al*. (2001) tested the antibacterial action of an ethanolic extract of *M. vulgare* against *Salmonella enteritis*, *Salmonella gallinarum*, *Streptococcus dysgalatiae*, *Streptococcus agalactiae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *E. coli (*agar diffusion test). 50 g of dried plant material were extracted with 250 ml of 80% ethanol and evaporated to dryness. The extract of *M. vulgare* had a minimum inhibitory concentration (MIC) of 4 mg/ml in *K. pneumoniae* and 1 mg/ml in *S. aureus*.

Al-Bakri *et al*. (2007) evaluated the antimicrobial activity of an ethanolic extract of *M. vulgare* by rapid XTT colorimetry and bacterial enumeration. 2.5 g powdered plant material was extracted with 25 ml ethanol (no further information). The extract was dried and dissolved in DMSO to a final stock concentration of 20 mg/ml. The extract exhibited antimicrobial activity against *Bacillus subtilis and S. aureus.*

Kunduhoglu *et al*. (2011) showed that the crude ethanolic extract (10 g powdered plant material extracted by Soxhlet extractor, no further information, 100 mg dry extract/ml stock solution) had antimicrobial effect (zone diameters 8-12) toward only a limited number of Gram-positive bacteria. The authors concluded that the dissimilar results observed to Al-Bakri *et al*. (2007) may be attributed to differences in techniques employed and extracts used.

Kanyonga *et al*. (2001) studied the *in vitro* antibacterial activity of a methanolic extract of *M. vulgare* (no DER information) at 50, 100, 200, 400 and 600 mg/ml by disc diffusion method. The study revealed that the extract showed a dose dependent effect against *B. subtilis*, *Staphylococcus epidermidis*, *S. aureus* and *Candida albicans* and moderately effective against *Proteus vulgaris* and *E. coli* while ineffective in the case of *Pseudomonas aeruginosa*.

Ramos-Guerra *et al*. (2007) determined the *in vitro* activity of the acetonic and methanolic extract (prepared by maceration, no further information) from *M. vulgare* against *Entamoebia histolytica* and *Giardia lamblia*, the causal agents of amoebiasis and giardiasis. The extracts were very active against *E. histolytica* ($IC_{50}$=7 and 12 µg/ml) and slightly moderate toxic to *G. lamblia*. The aqueous extract was not active.

Robles-Zepeta *et al*. (2011) evaluated the anti-*Helicobacter pylori* activity of the methanolic extract of *M. vulgare* by using the broth microdilution method. The dry plant material was extracted with methanol (1:10), dried and dissolved in DMSO to a final concentration of 10 mg/ml. The 50% MIC was higher than 800 µg/ml.

Diuretic activity

El Bardai *et al*. (2001) examined the pharmacological evidence of hypotensive activity of *M. vulgare* in spontaneously hypertensive rat (SHR) (210±mm Hg) and normotensive Wistar-Kyoto rats (WKY) (156±mm Hg). The aqueous extract was prepared by boiling 5 g of Marrubii herba in 100 ml water, after lyophilisation the yield was approximately 16% (w/w) (DER ~6.2:1). The rats were given 80 mg extract/kg/day orally, once a day by gavage, for 5 days. The treatment of SHR produced

only a small effect on urine volume at the beginning of the treatment, which vanished after 3 days and had no effect either on electrolytes or on creatinine and urea excretion. It did not affect diuresis and electrolyte excretion significantly in normotensive rats.

Antihyperglycaemic effects

Roman Ramos *et al*. (1992) tested the hypoglycaemic effect of an aqueous extract of *M. vulgare* in healthy rabbits with the gastric administration of water (4 ml/kg), tolbutamide (20 mg/kg) or the extract (132 g of the dried plant was boiled in 1 l water; 4 ml/kg). Temporary hyperglycaemia was induced by s.c. injection of 50% dextrose solution. After 60 min blood glucose was determined every 60 min for a period of 5 h. Both tolbutamide and the extract decreased significantly the hyperglycaemia as compared with control test (water). The extract was not statistically different from 20 mg/kg of tolbutamide.

Novaes *et al*. (2001) studied the hypoglycaemic effect of *M. vulgare* on alloxan-induced diabetic rats. The extract was prepared by maceration with ethanol at room temperature for approximately 10 days (no DER information). The reference drug was alloxan monohydrate (100 mg/kg; i.p.). The extract (300 mg/kg) was intragastrically administered to diabetic rats. The results showed that *M. vulgare* caused moderate effects, with inhibition rates of 30.3%.

Boudjelal *et al*. (2012) conducted a series of *in vivo* experiments in albino Wistar rats concerning the anti-diabetic effect of *M. vulgare*. Diabetes was induced in the animals by i.p. injection of alloxan. They were treated twice a day with aqueous extract (6 g Marrubii herba in 25 ml boiling water) with 100, 200 and 300 mg/kg and glibenclamide (5 mg/kg) for 15 days. The results indicate that administration of the aqueous extract at 200 and 300 mg/kg/twice daily for 2 weeks showed the best decrease in the blood glucose level (more than 60%), comparable to the effects of glibenclamide. A decrease of 50% was observed in the 100 mg dose group. The total lipids, triglycerides and total cholesterol were decreased, without attaining the values of the normal control.

Antioxidative effects

VanderJagt *et al*. (2001) analysed the total antioxidant capacity of aqueous extracts of *M. vulgare* (2 g dried plant extracted with 40 ml water) using a two-stage Trolox based assay. The antioxidant content of the aqueous extracts was 560 µmol/g Trolox equivalent/g dry weight.

Berrougui *et al*. (2006) elucidated the properties of a methanolic extract of *M. vulgare* (40% methanol, no DER information) towards cardiovascular disease by protecting human-low density lipoproteins (LDL) against lipid peroxidation and promoting high density lipoproteins (HDL)-mediated cholesterol efflux. Human-LDL were oxidised by incubation with $CuSO_4$ in the presence of increased concentrations of the extract (0-100 µg/ml). LDL lipid peroxidation was evaluated by conjugated diene formation, vitamin E disappearance as well as LDL-electrophoretic mobility. HDL-mediated cholesterol efflux assay was carried out in human THP-1 macrophages. Incubation of LDL with the extract significantly prolonged the lag phase ($P=0.014$), lowered the progression rate of lipid peroxidation ($P=0.004$), reduced the disappearance of vitamin E and the electrophoretic mobility in a dose-dependent manner. Also, incubation of HDL with the extract significantly increased HDL-mediated cholesterol efflux from THP-1 macrophages implicating an independent ATP binding cassette A1 (ABCA1) pathways.

Anticancer effects

Yamaguchi *et al*. (2006) explored the effects of *M. vulgare* leaves extract on anti-tumourigenicity of human colorectal cancer cells. The plant material (20 g) were extracted with 200 ml methanol for 48 h (DER 1:10). The extract was concentrated and dried. In a concentration of 250 µg/ml it caused apoptosis and cell growth suppression in human colorectal cancer cells and up regulated pro-apoptic non-steroidal anti-inflammatory drug-activated gene (NAG-1) through transactivation of the NAG-1 promoter.

*Assessor´s comment*

*The interpretation of the results from antimicrobial/anti-infective testing for clinical relevance is limited, because of the difference to therapeutic used extracts and the unknown DER in the majority of the extracts, which also may cause the differences in inhibition. There is at the present not sufficient evidence to suggest an antimicrobial/anti-infective activity of the preparations used clinically.*

*The interpretation of clinical relevance of small diuretic effects seen in spontaneously hypertensive rats and antihyperglycaemic effects in rabbits and rats is limited, partially also because of the application way. Furthermore, in the clinical study by Herrera-Arellano et al. (2004), no hypoglycaemic effect was found (see section 4.1.1).*

*An antioxidative effect of extracts of M. vulgare was shown in vitro. The in vitro tests are no sufficient scientific evidence for a conclusion of a beneficial clinical effect. Furthermore, there is presently no sufficient evidence to suggest an anticancer effect of Marrubii herba.*

**Isolated compounds**

Effect on vasorelaxant effects

El Bardai *et al*. (2003a) examined the compounds responsible for the vasorelaxant activity ascribed to the crude aqueous extract of *M. vulgare*, herba. Marrubii herba (60 g) was extracted with 400 ml distilled water at 90ºC for 15 min. The extract was divided in an aqueous fraction and an cyclohexane fraction. Pre-incubation of rat aorta with the cyclohexane fraction evoked a dose-dependent inhibition of KCl-induced contraction while the aqueous fraction showed no effect. Marrubenol and marrubiin were isolated. Marrubenol and marrubiin inhibited the contraction in concentration-dependent manner in rat aorta. Marrubenol was slightly more potent than marrubiin ($IC_{50}$ values were 7.7±1.9 µM and 24±2.3 µM, respectively). Both compounds were significantly less potent than verapamil.

El Bardai *et al*. (2003b) investigated the mechanism of the relaxant activity of marrubenol. Marrubenol inhibits contraction of rat arteries by blocking L-type voltage-dependent calcium channels in smooth muscle cells. The relaxing effect of marrubenol on rat aorta was unaffected by removal of the endothelium ($IC_{50}$ values were 11.8±0.3 µM and maximum relaxation 93.4±0.6 µM). Marrubenol also inhibited the contraction induced by noradrenaline (1 µM) in aorta, moreover was ineffective in aorta contracted by noradrenaline in the presence of 1 µM of $Ca^{2+}$ channel blocker nimodipine. In patch-clamp data obtained in aortic smooth muscle cells (A7r5) indicated that marrubenol inhibited $Ca^{2+}$ inward current in a voltage-dependent manner. The voltage-dependency may be the cause of its higher potency in smooth muscle compared to the heart, where contraction was unaffected up to 100 µM.

El Bardai *et al*. (2004a) described the precise site of interaction on the L-type channels in smooth muscle cells. In the study the authors investigated the interaction of marrubenol with “classical” binding sites for calcium antagonists, namely 1,4-dihydropyridines and phenylalkylamines, in rat intestinal muscle membranes. Competition binding studies indicate that marrubenol was a weak inhibitor of 1,4-dihydropyridine binding in membranes isolated from intestinal smooth muscle. As marrubenol inhibited the concentration evoked by KCl depolarization of intestinal smooth muscle half-maximally at a concentration of circa 12 µM, the interaction with the phenylakylamine binding site seems to account for the inhibition of L-type $Ca^{2+}$ channels by marrubenol. In contrast to mibefradil, marrubenol does not seem to interact with T-type $Ca^{2+}$ channels. The results of the study are limited because the study was performed with intestinal smooth muscle cells and not aorta membranes and as isolated substances were tested.

Antioxidative effects

Martin-Nizard *et al*. (2003) examined the protective effect of five natural polyphenols isolated from the aerial parts of *M. vulgare* against oxidised LDL induced cytotoxicity in bovine aortic endothelial cells. Four phenylpropanoid glycosides (acteoside, forsynthoside B, arenarioside, ballotetroside) and one non-glycosidic derivative (caffeoyl-1-malic acid) were tested. These compounds inhibited both copper and 2.2-azobis(2-amidinopropane) dihydrochloride-induced *in vitro* LDL oxidation and preserved the morphological aspects of the cells during their incubation with oxidised LDL.

Martin-Nizard *et al*. (2004) tested the effect of four natural phenolic compounds isolated from the aerial parts of *M. vulgare* (phenylpropanoid glycosides: acteoside, forsynthoside B, arenarioside, ballotetroside) against copper-oxidised LDL- induced Endotthelien-1 (ET-1) liberation by bovine aortic endothelial cells. The compounds inhibited *in vitro* the increase of the potent vasoconstrictor ET-1 when cells were incubated with Cu-LDL.

*Assessor´s comment*
*Assessing the results of the in vitro studies there is presently no sufficient evidence to acknowledge a vasorelaxant or antioxidant effect of preparations of M. vulgare.*

**Safety Pharmacology**

No information available concerning safety pharmacological studies.

Effect on systolic blood pressure/ antihypertensive effects
El Bardai *et al*. (2001) examined the pharmacological evidence of hypotensive activity of *M. vulgare* in SHR rats (210±mm Hg) and normotensive WKY rats (156±mm Hg). The aqueous extract was prepares by boiling 5 g of Marrubii herba in 100 ml water, after lyophilisation the yield was approximately 16% (w/w) (DER ~6.2:1). The rats were given 80 mg extract/kg/day oral, once a day by gavage, for five days. The extract significantly decreased the systolic blood pressure (SBP) in spontaneous hypertensive rat. The hypotensive effect was detectable from day 2 and was maximal at day 4 and 5. At the end of the treatment, the systolic blood pressure remained significantly lower than the pre-treatment value for 2 days and progressively increased. In normotensive rats, the SBP was not significant different to placebo.
The *ex vivo* effect of the extract was examined on contractile responses of the aorta. After treatment of SHR, the contractile response of aortic rings to 100 mM KCl solution was depressed by 19±3.4% ($n=14$, $p<0.05$). No effect was detected in normotensive rat aorta. The authors concluded that the characteristics of Marrubium actions are reminiscent of the effect of dihydropyridine Ca-channel blockers, these also selectively depress the SBP of hypertensive rats compared to normotensive rats.

El Bardai *et al*. (2004b) compared the effect of 10-week-long treatment with amlodipine or aqueous extract of *M. vulgare* and placebo on SBP, cardiovascular remodelling and vascular relaxation in SHR. The dosage of the extract was 80 mg/kg/day orally, once a day by gavage for rats from the age of 4 weeks up the 14$^{th}$ week. Both treatments produced similar decrease in SBP (37±2 mm Hg for amlodipine treated rats and 33±1 mm Hg for extract treated rats). Amlodipine treatment reduced left ventricle, aortic and mesenteric artery weight. Marrubium treatment had a significant antihypertrophic effect in aorta only. Relaxation to acetylcholine of mesenteric artery was improved by the extract but not by amlodipine treatment.

*Assessor´s comment*
*The administereddose (80 mg extract/kg) corresponds to a HED of 13 mg/kg (= 780 mg for a 60 kg adult = 4.8 g herbal substance). This is within the range of the human therapeutic doses of maximum 6 g herbal substance/day. The administeredsingle dose was higher than the human single dose (up to 2 g herbal substance). In the clinical study by Herrera-Arellano et al. (2004), no hypotensive effect was found (see section 4.1.1), therefore no hypotensive effect is expected at human therapeutic doses.*

**Pharmacodynamic interactions**

No information available.

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

No published data about pharmacokinetics are available.

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

**Single dose toxicity**

Oral administration

Jaouhari *et al*. (1999) carried out an acute toxicity study of the aqueous extract of *M. vulgare* on Swiss albino mice. The tested preparation was an infusion prepared of 1 g dried herb in 50 ml distilled water (DER 1:50). The extract was administered orally at a dose of 1 g/kg body weight. Animals were observed 7 days and changes in weight and behaviour were noted. On the eighth day the animals were sacrificed and an anatomo-histopathologic survey was undertaken. The mice treated with the extract showed tachycardia 1 h after intake of the infusion and loss of appetite 3 h after intake of the infusion. No histopathologic changes were seen.

De Oliveira *et al*. (2011) treated five female rats in an acute toxicity study orally with a single dose of 2,000 mg/kg extract of *M. vulgare* (1.5 kg plant material was macerated 7 days with 4 l methanol). On a period of 14 day the animals were observed. No changes could be detected in the skin, fur, eyes, mucous membrane (nasal), central nervous system and autonomic nervous system. The data suggest that the toxic dose of the *M. vulgare* methanolic extract is higher than 2,000 mg/kg. It would be classified in category 5 for toxicity under the criteria of the GHS (Globally Harmonized Classification System for Chemical Substances and Mixtures).

**Reproductive and developmental toxicity**

Kchouk & Chadli (1962) analysed the reproductive and developmental toxicity of a decoction from *M. vulgare* (no DER information) in 2 rats, 2 guinea pigs and 2 mice (approximately 2 ml/kg buccal or s.c.). The results showed a certain abortive activity in rats, whereas its abortive effect in guinea pigs and mice was not convincing. The authors concluded the data do not permit to extrapolate an abortive effect to humans.

## *3.4. Overall conclusions on non-clinical data*

Marrubii herba traditionally has been used as secretolytic drug and as bitter principle (amarum) in dyspeptic complaints and loss of appetite. In literature the expectorant action, possibly caused by stimulation of secretion from the mucous lining of the respiratory tract, is often attributed to marrubiin and the volatile oil. *Marrubium vulgare* herba has a bitter value of 3,000 (Blaschek *et al*., 2011). It is considered that Marrubium, as bitter principle, causes an increase of the gastric and biliary secretion and stimulates the appetite via activation of the bitter receptors.

Only a few studies exist which can be brought in connection with primary pharmacodynamic effects of *M. vulgare*. Antispasmodic, anti-inflammatory, analgesic and gastroprotective effects seem somehow plausible even though a direct correlation of the test results (kind of extract, route of administration, *in vitro* vs. *in vivo*) with the clinical situation is not possible. Effects on the stimulation of the appetite seem to be plausible by the knowledge about the processes initiated after the activation of bitter

receptors (Janssen *et al*., 2011), even though no studies for Marrubium preparations or its components exist. Pharmacodynamic studies which could prove expectorant effects could not be identified.
In *in vivo* experiments in rats, choleretic activity of marrubiinic acid was shown. The pharmacokinetics of marrubiin into marrubiinic acid and the concentrations needed for the pharmacological effect have not been investigated. Marrubiinic acid may contribute to the pharmacodynamic plausibility, but the clinical relevance is unclear. For some phenylpropanoid esters extracted from *M. vulgare* and marrubiin, anti-inflammatory and analgesic effects could be shown. Results are mostly of low relevance, as they were conducted *in vitro* or with i.p. administration. Furthermore there is no knowledge about the plasma concentrations of those substances in the clinical situation; therefore these results cannot make a contribution to the pharmacodynamic plausibility.
The effects which are classified as secondary pharmacodynamic effects of herbal preparations and/or isolated compounds (antimicrobial/anti-infective effects, diuretic effects in SHR, antihyperglycaemic effects, antioxidative effects, anticancer effects, vasorelaxant activity) are not well supported by the literature data (uncertainties concerning the extracts, *in vitro* situation or different route of application, concentrations used compared to clinical situation). Therefore they are seen as not relevant.

While no conventional studies concerning safety pharmacology were found, two studies in rats suggest a hypotensive effects (in spontaneous hypertensive rats) and antihypertrophic effects in the aorta. From the long-standing use of preparations from *M. vulgare*, there is presently no sufficient evidence to confirm such hypotensive effects. Studies concerning safety pharmacodynamic interactions were not found.

No published data about pharmacokinetics are available.

No data from investigations concerning single- and repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from Marrubii herba in animals, according to current state-of–the-art standards are available. The requirements for a Community list entry are not fulfilled.

# 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

Herrera-Arellano *et al*. (2004): In a randomised, double-blind and controlled trial, the clinical effect of an aqueous extract from *Cecropia obtusifolia* or from *Marrubium vulgare* on blood glucose and serum lipids was analysed in patients with type 2 diabetes and a poor response to conventional medical treatment. All patients included showed blood glucose ≥140 mg/dl, independently of cholesterol and triglycerides level and were treated with glibenclamide at different dosage. A total of 43 patients were divided in two groups. The patients were to prepare an infusion with 1 g filter-paper sachets in a cup of boiling water three times a day before every meal (daily dose 3 g drug). After 21 days of treatment the fasting glucose values were reduced by 15.25%, cholesterol and triglycerides were increased by 14.62% and 42.0% in patients treated with *C. obtusifolia*. In the case of patients treated with *M. vulgare*, the plasma glucose level was reduced by 0.64% and cholesterol and triglycerides by 4.16% and 5.78% respectively. The effect produced by the extract from *M. vulgare* was minimal and contrasts that in the above-mentioned study in healthy rabbits (Roman Ramos *et al*., 1992).
The treatment evaluated did not produce important modifications of the parameters that measure the renal function. The serum levels of creatinine and urea did not show pathologic alterations at the end of the study. In some patients, the treatment produced only mild and temporary side effects, for which

it was not necessary to interrupt the treatment. In the group of *M. vulgare*, five side effects occurred: nausea, oral dryness, sialorrhea, dizziness and anorexia, while in the group of *C. obtusifolia* three side effects were reported: excessive salivary flow, exhaustion and pyrosis.

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

No human data available.

## 4.2. Clinical Efficacy

### 4.2.1. Dose response studies

Dose response studies have not been performed.

### 4.2.2. Clinical studies (case studies and clinical trials)

Ballero *et al*. (1998): Ethnopharmacobotanical studies carried out in northern Sardinia have confirmed the use of *Marrubium vulgare* in the prevention and treatment of asthmatic syndrome. For acute asthma a decoction of *M. vulgare* was given. For a preventive treatment for asthma a decoction of fresh leaves of *M. vulgare* together with *Cynodon dactylon* leaves was administered at spring or all through the year in cases of perennial asthma. The decoction for the prevention of asthmatic fits was administered in one dose (a glass of 25-30 ml) on an empty stomach in the morning. The efficacy of the preparation of *M. vulgare* in the preventive treatment and cure of acute asthmatic fits reported by five patients was evaluated with an accurate case history and clinical examination of each patient. These confirmed an improvement in the general state of health of the subject. The authors hypothesised that the action may be attributed to the presence of flavonoids in the decoctions. Like the flavonoids in *M. vulgare*, disodium cromoglycate possesses the structural nucleus of benzo-µ-pirone. The authors concluded that flavonoids could act by inhibiting the release of anaphylactic, and therefore inflammatory mediators, with an inhibitory potency comparable to that of disodium cromoglycate, but with an additional, valuable action, i.e. that of inducing the relaxation of the bronchial smooth muscle.

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

No human data from clinical studies in children or elderly are available. For some marketed preparations, a dosage is recommended for adolescents above 12 years of age. Due to the lack of sufficient data, the use in children under 12 years of age is not recommended. In the absence of safety concerns, a posology is given in the monograph for use in adolescents, adults and elderly.

## *4.3. Overall conclusions on clinical pharmacology and efficacy*

The traditional use is well documented in literature and different European pharmacopoeias. The efficacy of the medicinal product is plausible on the basis of long-standing use and experience for the administration in adults and adolescents over 12 years of age for the indications:
- “Traditional herbal medicinal product used as an expectorant in cough associated with cold”,
- “Traditional herbal medicinal product for symptomatic treatment of mild dyspeptic complaints such as bloating and flatulence” and
- “Traditional herbal medicinal product used in temporary loss of appetite”.

Controlled clinical studies required to support a well-established use have not been performed with *Marrubium vulgare* preparations. The ethnopharmacobotanical study by Ballero *et al*. (1998) cannot

proof efficacy for acute asthma or as a preventive remedy for asthma. No conclusion for efficacy for specific indications is possible. The results of the study indicate that the use of Marrubium tea can be beneficial in the context of the use as an expectorant/anti-inflammatory in cough associated with cold.

Bitter preparations increase saliva and gastric secretion, therefore the efficacy in case of appetite loss can only be assumed in patients with a reduced gastric secretion. In patients with normal appetite, no increase can be expected (Hänsel, 1991; Tyler, 1994; Schilcher *et al*., 2007).

# 5. Clinical Safety/Pharmacovigilance

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

See section 4.1.1.

## *5.2. Patient exposure*

Apart from the medicinal use, *Marrubium vulgare* is also used as food e.g. in candies. There is no information available on the extent of this use.

## *5.3. Adverse events and serious adverse events and deaths*

**General data**

In phytotherapeutic books such as Bradley (1992), Blumenthal *et al*. (1998), Blaschek *et al*. (2006), no adverse events, serious adverse events and deaths are reported.

Carey (1962): In a list of occupational toxicity of cultivated flowers, that relates to the central states of the U.S., Horehound juice is listed as constituent that may induce contact dermatitis.

**Case reports in the EU Member States**

In the BfArM (Germany) database (28 June 2012), no adverse events are reported. No adverse events have been reported also by the other Member States during the preparation of the monograph.

**Published case reports**

Jayasekera *et al*. (2005): A 65-year-old man had a total hip arthroplasty. The immediate postoperative period was complicated by an acute wound haemorrhage. The patient received a 4-unit blood transfusion and the bleeding stopped after about 8 h. The patient had continued taking a herbal medicine containing *Gingko biloba, Piper lango, Marrubium vulgare* and *Citraria islandica* up to the day of surgery (no information about the preparations, DER, dosage). *Ginkgo biloba* is known to increases the risk of bleeding, especially used in combination with warfarin, antiplatelet drugs and certain other medication. Considering the unknown formulation and dosages, no conclusion can be drawn by this case report.

In the clinical study by Herrera-Arellano *et al*. (2004), after 21 days of treatment, five side effects (mild gastrointestinal reactions such as nausea, oral dryness, sialorrhea, dizziness and anorexia) were observed in a total of 21 patients who received glibenclamide together with a tea preparation of *M. vulgare* (1 g, 3 times daily). In the second treatment group with another herbal tea, three side effects occurred. No statistical difference was found. Rational analyses of the results are limited because the study was conducted with diabetic patients and glibenclamide was used as co-medication. Some of the side effects described are known side effects of glibenclamide. Therefore the side effects of the study are not taken into the monograph.

Assessor's comment

*No case reports are available in the databases of the Member States. Mild gastrointestinal reactions are reported within a clinical trial with 21 diabetic patients but are not mentioned in the monograph, because the patients received a co-medication (glibenclamide), for which some of the observed side effects are known. A clear analysis of the results is therefore not possible.*
*Like all herbal preparations with a traditional use as bitter remedy, Marrubium vulgare products increase the gastric acid secretion. Schilcher et al. (2007) recommend that bitter compounds (amara) with a bitter value over 10,000 should be contraindicated in patients with active peptic ulcer (e.g. Cynarae folium 10,000; Cinchonae cortex ≥12,000; Gentianae radix ≥10,000). As Marrubii herba has a lower bitter value (3,000), given that it shows gastroprotective effects in vivo and as no case reports are available, no absolute contraindication is necessary for this patient group; patients with active peptic ulcer should however consult a doctor before using Marrubii herba preparations.*

## *5.4. Laboratory findings*

Herrera-Arellano *et al*. (2004): After 21 days of treatment with *Marrubium vulgare* tea (3 g/day), the plasma glucose level was reduced by 0.64% and cholesterol and triglycerides by 4.16% and 5.78% respectively. The treatment evaluated did not produce important modifications of the parameters that measure the renal function. The serum levels of creatinine and urea did not show pathologic alterations at the end of the study.

No laboratory findings in relation to other *Marrubium vulgare* preparations are available.

## *5.5. Safety in special populations and situations*

**Use in children**

No clinical studies in children or elderly are available. In the marketed preparations, the dosages are recommended for adolescents above 12 years of age and adults. From the market information provided by the Member States during the preparation of the monograph, it was seen that some Marrubium products seem to be also used in children e.g. for lack of appetite. Due to the lack of sufficient data including dosages, the use is not recommended for children under 12 years of age.

**Drug interactions**

Based on data held at the Uppsala Monitoring Centre of the WHO (World Health Organization) that has the largest database on adverse drug reactions (ADRs), including herb-drug interactions, Williamson (2005) analysed interactions between herbal and conventional medicines. For *M. vulgare*, no effects on drug metabolising enzymes and P-glycoprotein (P-gp) were known and neither clinical nor pharmacological interactions were reported.

In phytotherapeutic books such as Bradley (1992), Blumenthal *et al*. (1998), Blaschek *et al*. (2006), interactions with other drugs are not mentioned.

**Use in pregnancy and lactation**

Ciganda *et al*. (2003): A descriptive retrospective survey was conducted on the calls received by the Montevideo Poison Centre (Uruguay), between 1986 and1999, concerning the ingestion of herbal infusion with an abortive intend. A total of 86 cases involving 30 different plant species had been identified. Marrubium was used in one case in a home-made mixture of several plants. Abortion occurred in 23 cases, but not in the case of Marrubium use. In the survey conclusion, Marrubium was not associated with an abortion.

Safety during pregnancy and lactation has not been established. There are no human data on effects of *Marrubium vulgare* preparations on the foetus. Animal studies (Kchouk & Chadli, 1962) showed a certain abortive activity in rats, whereas its abortive effect in guinea pigs and mice was not convincing.

In view of the absence of sufficient clinical data, the use of *M. vulgare* products during pregnancy and lactation is not recommended.

**Overdose**

According to List *et al*. (1976), in high dosages *Marrubium* can cause arrhythmia. No information about the "high dosages" or case reports are given. Theoretically "large amounts" of White Horehound may increase the risk of abnormal heart rhythms and should be avoided by people taking drugs that affect heart rhythm.

Schilcher *et al*. (2007) reported that "large" dosages of amara can lead to contradictory effects, such as inhibition of appetite and secretolysis, and can cause headache in sensitive patients.

From literature, monographs and databases of the Member States, no case reports on overdose of *M. vulgare* preparations are available. Therefore, it is stated in the monograph that no case of overdose has been reported.

**Drug abuse**

There are no reports on drug abuse in relation to the medicinal use of *M. vulgare* preparations.

**Withdrawal and rebound**

There are no reports on withdrawal and rebound in relation to the medicinal use of *M. vulgare* preparations.

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

No studies on the ability to drive and use machines have been performed. There are no reports on impairment of mental ability. No conclusions can be drawn on potential concern arising from effects on ability to drive or operate machinery by the known ingredients of *Marrubium vulgare*.

## *5.6. Overall conclusions on clinical safety*

The safety of use in defined conditions of *Marrubium vulgare* medicinal products can be derived from the long-standing use and experience. Apart from the medicinal use, *Marrubium vulgare* is also used as food e.g. in candies. In relevant phytotherapeutic books and in the databases of the Member States, no adverse events, serious adverse events and deaths have been reported. There are no case reports on overdose, drug interactions, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability. In the literature, it is described that "large" dosages of amara can lead to contradictory effects, such as inhibition of appetite and secretolysis, and can cause headache in sensitive patients. For *M. vulgare*, no effects on drug metabolising enzymes and P-gp are known and clinical and pharmacological interactions are not reported. Based on data from the Uppsala Monitoring Centre of the WHO, Williamson (2005) found no interactions between *M. vulgare* medicines and conventional medicines.

Limited data of laboratory findings during treatment with a *Marrubium vulgare* tea suggest that it did not produce important modifications in the plasma glucose level, cholesterol and triglycerides and the parameters that measure the renal function, serum levels of creatinine and urea.

On the basis of information on traditional use, Marrubii herba containing medicinal products prove not to be harmful in the specified conditions of use. The indications are appropriate for use in adolescents

over 12 years of age, in adults and in elderly without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment. The duration of use without medical advice is limited to one week for the first indication and to two weeks for the second and third indications found in the monograph.

*M. vulgare* preparations are contraindicated in patients with hypersensitivity to the active substance and to other plants of the Lamiaceae (Labiatae) family. Like all herbal preparations with bitter remedy, *M. vulgare* preparations are contraindicated in patients with obstruction of the bile duct, cholangitis, liver disease and ileus.

Patients with active peptic ulcer, gallstones and any other biliary disorders should consult a doctor before using Marrubii herba preparations.

Due to lack of data, the use is not recommended during pregnancy and lactation.

# 6. Overall conclusions

Based on the data documented in the assessment report, a Community herbal monograph is established on the traditional uses of several preparations from *Marrubium vulgare* L., herba. The traditional uses of *Marrubium vulgare* preparations fulfil 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. None of the data fulfils the requirements to demonstrate a well-established medicinal use with recognised efficacy for Marrubii herba preparations, thus the monograph is restricted to traditional uses. The efficacy is plausible on the basis of long-standing use and experience for the following indications:

Indication 1)
Traditional herbal medicinal product used as an expectorant in cough associated with cold.

Indication 2)
Traditional herbal medicinal product used for symptomatic treatment of mild dyspeptic complaints such as bloating and flatulence.

Indication 3)
Traditional herbal medicinal product used in temporary loss of appetite.

For the use in indications 2) and 3), the herbal preparation should be taken ½ hour before the meals.

**Benefit-Risk assessment**

The licensing of herbal medicinal product is subject to compliance with the requirements of a European Pharmacopoeia monograph. As an unambiguous macroscopic, microscopic, chemical identification of the herbal material is possible, adulteration/contamination of the herbal substance therefore is not expected.
In the databases of the Member States, no adverse events are reported. Mild gastrointestinal reactions were observed in a clinical study in diabetic patients, however the patients received a co-medication (glibenclamide), for which some of the side effects are known. No serious adverse events with a therapeutic posology of the herbal preparations are reported in the literature/reference sources with a well-documented history. Intoxications due to the herbal preparations are not reported in the literature/reference sources. No cases of overdose have been documented in the past 30 years. In the literature, it is described that “large dosages” of *M. vulgare* preparations may increase the risk of abnormal heart rhythms. In the literature, it is also described that “large” dosages of amara (bitter) can lead to contradictory effects, such as inhibition of appetite (anorexia) and inhibition of secretolysis, and can cause headache in sensitive patients.

There are no reports on drug interactions, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability. Limited data of laboratory findings during treatment with a *Marrubium vulgare* tea suggest that it did not produce important modifications in the plasma glucose level, cholesterol and triglycerides and the parameters that measure the renal function, serum levels of creatinine and urea.

No data from investigations of single- and repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from Marrubii herba in animals, according to current state-of–the-art standards are available. The toxic dose of a *Marrubium vulgare* methanolic extract seemed to be higher than 2,000 mg/kg.

The herbal preparations should not be used in patients with hypersensitivity to the active substance and to other plants of the Lamiaceae (Labiatae) family, obstruction of the bile duct, cholangitis, liver disease or ileus. Caution for use is necessary for patients with active peptic ulcer, gallstones and any other biliary disease.

The duration of use is limited because the preparation is intended and designed for use without the supervision of a medical practitioner ( one week for the indication 1) or two weeks for the indications 2) and 3). Due to lack of data, the use is not recommended during pregnancy and lactation. Marketed preparations are used at specified dosages in adults and adolescents above 12 years of age. Therefore the monograph establishes the use in these age groups as well as in elderly in the absence of safety concerns for the latter. Due to the lack of adequate data, the use is not recommended in children under 12 years of age.

There are therapeutic alternatives for the indication 1) from chemical preparations (such as ambroxol) to other herbal preparations (e.g. Thymi herba, Hederae helicis folium).
For the indications 2) and 3), there are therapeutic alternatives like other herbal preparations traditionally used in the context of a bitter remedy (e.g. Absinthii herba, Cichorii radix, Millefolii herba, Taraxaci radix cum herba).

It can be concluded that the benefit-risk assessment for *Marrubium vulgare* preparations included in the monograph is positive for the use as an expectorant in cough associated with cold, for symptomatic treatment of mild dyspeptic complaints such as bloating and flatulence and for the use in temporary loss of appetite, under the specified conditions of use and at the therapeutic dosages.

The therapeutic areas for browse search on the EMA website are “Cough and cold” and “Gastrointestinal disorders”.

Because the minimum required data on mutagenicity (AMES test) are not available for herbal preparations of Marrubii herba, an inclusion to the Community list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.

# Annex

## List of references