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European Medicines Agency
Evaluation of Medicines for Human Use

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**ASSESSMENT REPORT ON
VERBASCUM THAPSUS L., V. DENSIFLORUM BERTOL.; V. PHLOMOIDES L., FLOS
WITH TRADITIONAL USE**

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Superseded

I. REGULATORY STATUS OVERVIEW¹

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'

Member State	Regulatory Status				Comments ²
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Czech Republic	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Trad.
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Only combinations
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Liechtenstein	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Luxemburg	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Malta	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
The Netherlands	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Norway	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Poland	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Trad.
Portugal	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Romania	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Only combinations
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	

¹ This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

² Not mandatory field

Answered by Austria

Well-Established Use/ Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) None

Common name in respective national language: Königskerzenblüte

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Risks known?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
Pharmacovigilance actions taken?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
Herbal substance(s) / herbal preparation(s) on the market?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Risks known?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
Food Supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

Additional comments (e.g. information on relevant combination products):

There is no product authorized with Verbasci flos as the only active ingredient. However, numerous combinations are on the market, primarily mixtures of herbal substances for tea preparation (indication: cough), few medicinal products contain liquid extracts prepared with ethanol (DER 1:3, ethanol 70%) or aqueous extracts (DER similar to tea preparation).

Answered by Belgium

Well-Established Use/ Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) None

2)

3)

Verbascum thapsus: We have no medicinal products with verbascum as single ingredient.

Additional comments (e.g. information on relevant combination products):

Verbascum leaves & flowers are included in a combination product (herbal tea), 50mg/g tea. The MA dates from 1964.

Answered by Croatia

Common name in respective national language: Divizma, cvijet

Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) herbal drug

Since when are the Preparations on the market?

ad 1) not known

Pharmaceutical Form (Standard Terms)

ad 1) herbal tea

Posology (Route of administration in Standard Terms + daily dosage)

ad 1) oral (DD not known)

Indications

ad 1) common cold, cough, laryngitis (expectorant)

Risks (adverse drug effects, literature)

ad 1) not known

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation?

Yes No

Herbal substance(s) / herbal preparation(s) on the market?

Yes No

Risks known?

Yes No

Food Supplement?

Yes No

Answered by the Czech Republic

Common name in respective national language:

Traditional Use

Indications: adjuvant in acute and chronic upper respiratory tract catarrhs

Preparations (kind of extract, extraction solvent, DER)

Combination product registered in the Czech Republic:

Herbal tea containing Verbasci flos (8 %), Foeniculi fructus (5 %), Liquiritiae radix (10 %), Plantaginis folium (23 %), Menthae piperitae herba (10 %), Farfarae folium (22 %), Althaeae radix (22 %)

Since when are the Preparations on the market?

The combination product has been on the market since 1969

Pharmaceutical Form (Standard Terms)

For oral use and for gurgling

Posology (Route of administration in Standard Terms + daily dosage)

According to the current version of the Czech Pharmacopoeia: single dose 1.5 g, daily dose 3.0 – 4.5 g

Additional comments:

Verbasci flos has been a subject of Czechoslovak/Czech Pharmacopoeia since 1970

Answered by Denmark

Common name in respective national language: Filtbladet kongelys

No products on the market with *V. thapsus*, but with two other species

Well established Use

1) Bronikyl. Extractum verbasum flos (2,5:1) – from *Verbasum densiflorum* or *V. phlomoides* L. 1 ml contains extract corresponding to 8,6 mg flower.

2) Bronikyl. Extractum verbasum flos (2,5:1) from *Verbasum densiflorum* or *V. phlomoides* L. 1 tablet contains extract corresponding to 128 mg flower (and *Primula radix* corresponding to 47,5 mg radix)

Since when are the Preparations on the market?

ad 1) Between 1997 and 1 December 2000

ad 2) Between 1997 and 1. December 2000

Pharmaceutical Form (Standard Terms)

ad 1) Oral solution

ad 2) Tablets

Posology (Route of administration in Standard Terms + daily dosage)

ad 1) Adults: 1-2 spoons (15-30 ml) 3 times daily.

Children 6-12 year: 1-2 spoons (15-30 ml) 2 times daily.

ad 2) Adults: 1-2 tablets 3 times daily. Children 6-12 years: 1-2 tablets 2 times daily.

Indications

ad 1) R05. Expectorant in shorter periods of cough ad 2) R05.

Risks (adverse drug effects, literature)

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation? Yes No

Herbal substance(s) / herbal preparation(s) on the market? Yes No

Risks known? Yes No

Food Supplement? Yes No

Additional comments (e.g. information on relevant combination products):

The product Bronikyl is a combination product with Extractum *primula radix* (3,3:1) (*Primula veris* L./*Primula elatior* L.).

In food supplements:

Verbasum densiflorum Bertol. [*Verbasum thapsiforme* Schrad.] and *Verbasum phlomoides* L. Up to 200 mg is accepted in food supplements.

Answered by Germany

Common name in respective national language: Königskerzenblüten, Wollblumen

Well-Established Use/Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) None

Additional comments (e.g. information on relevant combination products):

According the European Pharmacopoeia 5.07 *Verbasci flos* is not only defined as the flowers of *Verbascum thapsus* but as the dried flower, reduced to the corolla and the androecium, of *Verbascum thapsus*, *V. densiflorum* and *V. phlomoides*.

Since 1996 exists a Standard Marketing Authorisation for the herbal substance *Verbascum thapsiforme* and *Verbascum phlomoides*. It is defined as herbal tea. Indication: catarrh of the upper respiratory tract. Daily dosage: 3-4 x a day 1 g drug on 150 ml.

Traditional use:

There are 10 medicinal products that contain *Verbasci flos* (drug or extract) in combination with other active substances like: e.g. *Thymus vulgaris*, *Plantago lanceolata herba*, *Tiliae flos*, *Cetaria islandica*, *Primulae radix*, *Anisii fructus*, *Foeniculi fructus*, *Menthae piperitae folium*, *Salviae folium*, *Pini turiones*, *Lamii albi flos*, *Polygoni avicularis herba*. These products are on the German market since 1978.

well-established use:

There are no medicinal products on the German market that contain *Verbasci flos* as an active substance. There are 2 medicinal products that contain *Verbasci flos* as an excipient (on German market since 1978).

Answered by Ireland

Well-Established Use/ Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) None

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation? Yes No

Risks known? Yes No

Pharmacovigilance actions taken? Yes No

Herbal substance(s) / herbal preparation(s) on the market? Yes No

Risks known? Yes No

Food Supplement? Yes No

Additional comments (e.g. information on relevant combination products):

We have no combination products approved as medicines in Ireland.

We have no adverse reactions associated with *Verbascum thapsus*, either alone or in combination, on our national database.

Answered by Latvia

Common name in Latvian: parastā deviņvīruspēka ziedi

Well-Established Use/Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) None

Additional comments (e.g. information on relevant combination products):

Traditional use:

Internally. As a demulcent and expectorant for treatment of hoarseness, inflammation of the upper respiratory tract, bronchitis, tracheitis, pertussis, influenza and common cold.

In the folk-medicine:

Internally. For treatment of bronchial asthma, lung tuberculosis, irritable bowel syndrome, impaired liver and spleen functions, metabolism disorders, as a diaphoretic.

Externally for the bath in cases of skin irritation, rachitis and scrofula, for topical application in cases of abscesses, ulcers and purulent wounds. Dry flower-powder – for the sprinkle of chaped skin.

Answered by Poland

Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) Verbasci flos

2) Verbasci flos

3) Verbasci flos

4) Sirupus Verbasci. Prepared traditionally by adding 1,6 sugar to 1 kg fresh flowers. Standardised on content of not less than 0,0025% of aucubin.

5) Sirupus Verbasci containing 15% of Verbasci flos extractum (1:5), ethanol 60%.

6) Sirup containing Verbasci floris extractum fluidum 15%. Standardised on not less than 0,02% of aucubin

Since when are the preparations on the market?

1) 1995

2) 1995

3) 2002

4) 1997

5) 1997

6) 2001

Pharmaceutical form (Standard Terms)

1) herbal tea

2) herbal tea

3) herbal tea

4) Sirup

5) Sirup

6) Sirup

Posology (Route of administration in Standard Terms + daily dosage)

- 1) Preparation of decoct: to 1 spoon of dried flowers add 200ml of water, heat to boil, strain and wait 10-15 min. for lowering temperature. Drink ½ glass of warm decoct, 2 – 3 times daily.
- 2) Preparation of decoct: to 1 spoon of dried flowers add 200ml of water, heat to boil, strain and wait 10-15 min. for lowering temperature. Drink ½ glass of warm decoct, 2 – 3 times daily.
- 3) Preparation of decoct: to 1 spoon of dried flowers add 200ml of water, heat to boil, strain and wait 10-15 min. for lowering temperature. Drink ½ glass of warm decoct, 2 – 3 times daily.
- 4) Adults: 1-2 spoons, 3 x daily. Children: 1-2 teaspoons 3 x daily.
- 5) Adults: 15ml 3 x 4 times daily. Children over 6 years old: 5ml 2 x 3 daily.
- 6) Adults: 3-4 x 1 teaspoon or 2 x spoon daily. Children over 6 years old. 3 – 4 x teaspoon daily.

Indications

- 1) Decoct is used in soothing and mild expectorant in upper airways diseases.
- 2) Decoct is used in soothing and mild expectorant in upper airways diseases.
- 3) Decoct is used in soothing and mild expectorant in upper airways diseases.
- 4) Soothing and mild expectorant in cough and catarrhs of mouth, throat and bronchial mucosa. As an aid in common cold, flu and pharyngitis and bronchitis.
- 5) Preparation used traditionally in pharyngitis, upper airways inflammations and as supporting expectorant.
- 6) As an aid in upper airways diseases and pharyngitis (ex in flu with symptoms of hoarseness and dry cough). Traditionally used as expectorant and soothing.

Risks (adverse drug effects, literature)

- 1) None reported
- 2) None reported
- 3) None reported
- 4) None reported
- 5) None reported
- 6) Not known

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation? Yes No
Herbal substance(s) / herbal preparation(s) on the market? Yes No
Risks known? Yes No
Food Supplement? Yes No

Answered by Slovenia**Common name in respective national language:** cvet drobnocvetnega lučnika**Traditional Use***Preparations (kind of extract, extraction solvent, DER)

1) liquid extract; extraction solvent: ethanol (combination product)

Since when are the Preparations on the market?

ad 1) 02.02.1993

Pharmaceutical Form (Standard Terms)

ad 1) oral solution

Posology (Route of administration in Standard Terms + daily dosage)

ad 1) oral use: 5 ml two to three times per day

Indications

ad 1) mitigation of digestive problems

Risks (adverse drug effects, literature)

ad 1) /

Herbal substance(s) / herbal preparation(s) on the market? Yes No

Risks known?

 Yes No

Food Supplement?

 Yes No**Additional comments (e.g. information on relevant combination products):**

Verbascum flos is one of the active ingredients in medicinal product Pervivo® (oral solution).

1000 ml of liquid extract contains:

Curcuma zedoaria Rosc., radix	1,380 g
Angelicae radix korenina zdravilnega gozdnega korena	1,360 g
Fraxinus ornus L., exudatum izlo_ek malega jesena (mana)	1,360 g
Myrrha	0,700 g
Carlina acaulis L., radix	0,680 g
Gentianae radix	0,500 g
Myristica fragrans Houtt.	0,280 g
Liquiritiae radix	0,170 g
Menyanthidis trifoliatae folium	0,120 g
Acorus calamus L., rhizoma	0,047 g
Anisi stellati fructus	0,046 g
Citrus aurantium subsp. amara Engl., pericarpium (in insula Curacao coluntur)	0,038 g
Absinthii herba	0,035 g
Citrus aurantium subsp. amara Engl., pericarpium	0,031 g
Caryophylli flos	0,030 g
Inula helenium L., radix	0,020 g
Piper cubeba L., fructus	0,017 g
Cnicus benedictus L., herba	0,015 g
Zingiberis rhizoma	0,015 g
Langusa galanga (L.) Stuntz., rhizoma	0,014 g
Verbasci flos	0,014 g
Centaurii herba zel navadne tavžentrože	0,013 g
Citrus sinensis Osbeck., pericarpium	0,011 g
Achillea moschata Wulf., herba	0,006 g
Iris germanica L., herba	0,005 g
camphora racemica	0,950 g
theriak	0,970 g

*Product has a normal marketing authorisation for the moment. But it is foreseen that it will be changed to traditional use registration till the end of this year when revision of old products should be finished.

II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

VERBASCI FLOS

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED (TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Verbascum thapsus</i> L., <i>V. densiflorum</i> Bertol. (<i>V. thapsiforme</i> Schrad), and <i>V. phlomoides</i> L., flos (mullein flower)
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Herbal substance or herbal preparation as herbal tea for oral use
Rapporteur	Pharm. Gro Fossum
Assessor(s)	Prof. Karl Egil Malterud Pharm. Asefeh Moradi

II.1 INTRODUCTION

II.1.1 Description of the herbal substance(s)

Mullein flower consists of the dried flowers, reduced to the corolla and the androecium, of *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad), and *V. phlomoides* L. (Ph. Eur. 2008). German pharmacopeial grade mullein flower must have a swelling index of not less than 9 and it must contain not more than 5% calices and discoloured flowers (brown corollas) (Blumenthal 2000). The Swiss pharmacopeia requires a swelling index of not less than 12 (Blumenthal 2000).

In this report, the common expression “mullein flower” refers to the flowers of *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad), and *V. phlomoides* L. Unfortunately, in many references, specifications of which flower species they refer to, are not mentioned.

V. thapsiforme Schrad is broadly used as a synonym for *V. densiflorum* Bertol. in handbooks and scientific journals. According to Integrated Taxonomic Information System (Itis), *V. thapsiforme* taxonomic status as a synonym is not accepted. Based upon this, the synonym *V. thapsiforme* is replaced with *V. densiflorum* in this assessment report.

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

The traditional use of mullein goes back to ancient times. Mullein preparations were used during the Middle Ages for various diseases. According to Madaus (1938), Lonicerus (1564) paid tribute to mullein for its actions as an expectorant, heart- and fever medicine, and as a remedy against warts etc. The traditional use of mullein flowers has been thoroughly documented in several handbooks and scientific literature. Traditional medicinal use of mullein flower connected to catarrh of the upper respiratory tract, cough and colds has been documented in handbooks such as Madaus (1938), Hagers Handbuch (Blaschek et al. 2006), Wichtl (2004) and British Herbal Compendium (Bradley 2006).

Mullein flower is native to central-, eastern-, and southern Europe, Asia Minor, northern Africa, and Ethiopia. The material of commerce originates primarily from cultivated plants, and is imported from Egypt, Bulgaria, and Russia (Wichtl 2004). *Verbascum thapsus* is found throughout Europe and abundantly naturalised in the United States of America (USA). In Europe the tradition has been to use the flowers of *V. densiflorum* and *V. phlomoides*; these species are less common in the United Kingdom (UK) and not found in the USA although the flowers were at one time official in the U.S.N.F. (Bradley 2006). All the various species of mullein found in Britain possess similar medicinal properties, but *V. thapsus*, the species of most common occurrence, is the one most employed (Grieve 1974). Both the leaves and flowers of mullein have been used in folk medicine (Youngken 1943, Grieve 1974). The dried stems have also been used (Martindale 2007). Stems were dipped into suet or wax to make torches (Grieve 1974). According to Wichtl (2001) the British Herbal Pharmacopoeia (BHP) 1983 monograph were on the dried leaves and stems of great mullein. The monograph in BHP 1996 is only for mullein leaf. The root is also mentioned by some references (Grieve 1974), but the medicinal use of the root does not appear to be described in any of the handbooks. The seeds seem mainly to have to be utilized as piscicide for fishing (Wilhelm, 1974).

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s)

Compounds:

- Iridoid glycosides:** 0.56% in *V. phlomoides*, 0.13% in *V. densiflorum*, including aucubin, catalpol, 6-xylosylaucubin and 6-xylosylcatalpol. *V. densiflorum* flower contains 10-fold less aucubin but 2-fold more catalpol than *V. phlomoides* flower (Bradley 2006). Also, 6-(4''-p-coumaroyl)-xylosylaucubin (named phlomoide) and another iridoidester glycoside, specioside, occur in *V. phlomoides* flower (Bradley 2006).
- Flavonoids:** 0.57% in *V. phlomoides*, 0.22% in *V. densiflorum*, although up to 4% of flavonoids has been claimed (Bradley 2006).
In the flower of *V. thapsus ssp. thapsus*: 6-hydroxyluteolin 7-glucoside, 3'-methylquercetin and 7,4'-dihydroxyflavone 4'-rhamnoside (Bradley 2006).
In *V. densiflorum* flower: apigenin and luteolin and their 7-glucosides, quercetin 7-glucoside and 3,7-diglucoside, tamarixetin 7-rutinoside and diosmin (diosmetin 7-rutinoside), the glycosides of luteolin and quercetin being predominant (Bradley 2006).
In *V. phlomoides* flower: tamarixetin 7-rutinoside (predominant), tamarixetin 7-glucoside, apigenin and luteolin and their 7-glucosides, diosmin, chrysoeriol, eriodictyol, kaempferol, quercetin and rutin. The reported presence of hesperidin was not confirmed in a later investigation (Bradley 2006).
- Phenylethanoid glycosides:** Verbascoside (acteoside), ca. 0.6% in *V. densiflorum* flower, but only traces in *V. phlomoides* flower, traces of forsythoside B (verbascoside 6'-apioside) in both species (Bradley 2006).
- Triterpene saponins:** Verbascosaponin, a monodesmosidic oleanane saponin with an ether bridge between C13 and C-28 and a group of four neutral sugar residues at the 3-position, was first isolated in 1980 from *V. phlomoides* flower; The structure was revised in 1992. The closely-related verbascosaponin A, verbascosaponin B and desrhamnosyl verbascosaponin have also been isolated from *V. phlomoides* (Bradley 2006).
In *V. thapsus* flower: four saponins of fairly similar structure have been isolated and named thapsuins A and B, and hydroxythapsuins A and B (Bradley 2006).
In *V. densiflorum* flower: No saponins have been confirmed in *V. densiflorum* flowers (Bradley 2006).

Hagers Handbuch has given a value for the saponin content in flowers of *Verbascum phlomoides* of 0.007% (Blaschek et al. 2006). This number is based on an article by Tschesche et al (1980). This is not a chemical analytical article, and the saponin determination described has limitations, e.g. it is not specified whether dry or fresh herb is used, and the extraction

and purification methods are prone to result in loss of substance. The European Pharmacopoeia has not mentioned the saponin content, and we have so far not found other articles estimating the saponin content in a more reliable way.

Saponins have the ability to cause haemolysis of blood *in vitro*. Low concentrations of saponins are capable of destroying erythrocyte membranes, causing a release of haemoglobin. The sensitivity of red blood cells to saponins has led to the widespread use of haemolysis as a quantitative determination method, with the haemolytic index defined as $30\,000 \times a/b$ (where *a* is the quantity of standard saponin (in grams) required for complete haemolysis of blood and *b* is the quantity of test saponin (in grams) required for complete haemolysis) (Hostettmann and Marston 1995). Although the haemolytic index cannot be an adequate alternative to the chromatographic methods for quantification of saponins, it gives an estimation of the saponin content. As described by Hostettmann and Marston (1995), haemolytic activity varies considerably with the structure of the glycoside. Monodesmosidic steroid and triterpene saponins (except acylglycosides and glycyrrhizin) are strongly haemolytic. According to Wichtl (2004), the haemolytic index of mullein flower saponins is about 350.

- Polysaccharides: 2-3%. Water-soluble acidic polysaccharides, principally a highly-branched arabinogalactan with a β -1,6-linked galactan backbone (MW 70,000), and neutral polysaccharides (an arabinogalactan and a xyloglucan) have been isolated from commercial mullein flower (*V. phlomoides* and/or *V. densiflorum*) (Bradley 2006). The European Pharmacopoeia 6.0 includes a test for swelling index with minimum 9.
- Phenolic acids: Vanillic, *p*-hydroxybenzoic, *p*-coumaric, ferulic, protocatechuic and *p*-hydroxycinnamic acids have been identified in the flowers of *V. densiflorum* and *V. phlomoides* (Bradley 2006). Also *p*-coumaric acid glucoside have been found in *V. phlomoides* flower (Bradley 2006).
- Other constituents: Phytosterols (β -sitosterol and ergosterol peroxide) and oleanolic acid in *V. thapsus* flower; phytosterol glycosides and digiprolactone (a bicyclic monoterpene) in *V. phlomoides* flower, fixed oil in flowers of *V. phlomoides* (2.4%) and *V. densiflorum* (1.6%), in which the main fatty acids are palmitic and linolenic acids; amino acids and free sugars in *V. densiflorum* flower; carotenoids and xanthophylls (Bradley 2006).

Pharmacodynamics

In vitro experiments

The following have been tested:

Antibacterial activity

A study done by Turker and Camper (2002) showed that a commercial product FO-Com (Flowers extracted of *V. thapsus* in pure olive oil), had antibacterial activity against *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This activity was attributed to the saponins.

Antiviral activity

A lyophilized infusion from *V. densiflorum* flower exhibited antiviral activity against several influenza A strains, an influenza B strain and fowl plague virus (Zgórnjak-Nowosielska et al. 1991). It also showed virucidal activity against *Herpes simplex* virus type 1. Influenza viruses titer decreased by 1-3 log units, while that of *Herpes simplex* virus decreased by 2.3 log. *V. densiflorum* flower showed virucidal activity on *Herpes simplex* virus at 300 µg/ml, but did not inactivate influenza viruses. The active substance was not specified in the study (Zgórnjak-Nowosielska et al. 1991).

An earlier study also demonstrated antiviral activity of mullein flower (*V. thapsus*) decoction, which at a concentration of 1% reduced the titer of A₂ type influenza virus by 4.9 log. Mullein flower also showed suppressive effects on B type influenza virus, reducing the virus titer by 2.5 log (Skwarek 1979).

Furthermore, an infusion prepared from flowers of *V. densiflorum* reduced the infectious and haemagglutination yields of a range of influenza viruses in tissue cultures. The combined application of *V. densiflorum* and three amantadine derivatives (drugs used in the prophylaxis and treatment of influenza A virus infections) resulted in a marked enhancement of the inhibitory effect of *V. densiflorum* infusion on the reproduction of influenza virus A/chicken/Germany/27, strain Weybridge (H7N7) in cell cultures of chicken embryo fibroblasts (Serkedjieva 2000).

A study done by Grzybek et al. (1997) showed that an ethyl acetate fraction from a methanolic extract of *V. densiflorum* flower inhibited HIV-1 reverse transcriptase by 39% at a concentration of 200 µg/ml.

Antitumor activity

The commercial product FO-Com (flowers extracted of *V. thapsus* in pure olive oil) showed antitumor activity (Turker and Camper 2002).

In screening for substances with antitumour activity, aqueous extracts from *V. densiflorum* flower had a strong inhibitory effect on the elongation step of protein biosynthesis in isolated rat liver microsomes. The saponin fraction was shown to be mainly responsible (Paszkiwicz-Gadek et al. 1990).

Mucociliary flow

The normal transport velocity of the isolated ciliated epithelium of the frog oesophagus was measured. Bromhexin increased this transport rate 1.34 fold and KNEIPP-Hustentee 1.38-fold. The different components of the cough tea had different effects on the mucociliary activity. In this *in vitro* study with the oesophagus epithelium of the frog, a water extract (6.4 g herbal drug / 100 ml) of Verbasci flos did not have any effect on mucociliary transport, whereas preparations from fennel and anis resulted in an increase of mucociliary transport. The study may be criticised because physical effects (increase in viscosity, ion concentration) were not taken into account. The authors stressed that other mechanisms, e.g. for saponins, may be responsible for an expectorant activity (Müller-Limmroth and Fröhlich 1980).

Pharmacological activities of constituents

Although relatively few pharmacological studies on mullein preparations have been reported, the pharmacological activities of certain constituents, notably the iridoid aucubin and the phenylethanoid glycoside verbascoside (acteoside), have been extensively studied and may explain some of the effects of mullein flower (Bradley 2006).

Aucubin:

Antiviral activity

Aucubin was found to suppress hepatitis B virus DNA replication *in vitro* in a cell culture system. Aucubin itself did not exhibit antiviral activity, but it showed significant activity when preincubated with β -glucosidase. Therefore, this result indicates that aucubin must be converted to its aglycone form to exhibit a significant antiviral activity (Chang 1997).

Verbascoside:

Anti-inflammatory activity

In a study by Xiong et al. (1999), verbascoside was found to have nitric oxide radical scavenging activity, which possibly contributes to its anti-inflammatory effect. Seven phenylethanoids, including acteoside (verbascoside) at the concentration of 100–200 μ M reduced (6.3–62.3%) nitrite accumulation in lipopolysaccharide (0.1 μ g/ml) stimulated J774.1 cells. At 200 μ M, they inhibited by 32.2–72.4% nitrite accumulation induced by lipopolysaccharide (0.1 μ g/ml)/ interferon- γ (100 U/ml) in mouse peritoneal exudate macrophages.

Furthermore, verbascoside inhibited formation of the 5-lipoxygenase product 5-HETE and leucotriene B₄ in human polymorphonuclear leukocytes. Verbascoside (acteoside) had strong radical scavenging actions (Kimura et al. 1987).

Cardiovascular activity

In isolated, perfused rat hearts (Langendorff model) verbascoside (1 μ M) increased heart rate by 37%, the force of contraction by 9% and coronary perfusion rate by 68%. Verbascoside significantly increased chronotropism ($p = 0.010$), inotropism ($p = 0.016$) and CPR ($p = 0.016$) when tested against the competitive α -adrenergic blocker phentolamine (1 μ M) (Pennacchio et al. 1999).

***In vivo* experiments**

Pharmacological activities of constituents

Aucubin:

Anti-inflammatory activity

Aucubin administered orally at 100 mg/kg inhibited carrageenan-induced rat paw oedema by 29.8% after 1 hour, 33% after 3 hours, and 20.7% after 5 hours ($p < 0.01$), compared to 34.2% inhibition by indometacin at 7 mg/kg after 1 hour, 44.4% after 3 hours and 12.2% after 5 hours. Aucubin administered topically at 1 mg/ear inhibited 12-O-tetradecanoylphorbol acetate (TPA)-induced mouse ear oedema by 80% after 4 hours ($p < 0.01$), compared to 87.1% inhibition by indometacin at 0.5 mg/ear (Recio et al. 1994).

Hepatoprotective activity

Aucubin administered intravenously at 100 mg/kg significantly protected beagle dogs from lethal poisoning caused by ingestion of *Amanita virosa* mushrooms. The activity of aucubin was partly due to a preventive effect on the depression of m-RNA biosynthesis in the liver caused by α -amanitin intoxication (Chang and Yamaura 1993).

It has also been reported that aucubin protected mice from hepatic damage induced by carbon tetrachloride intoxication (Chang et al. 1983).

Verbascoside:

Anti-inflammatory activity

Verbascoside's anti-inflammatory activity was evaluated by the carrageenin-induced paw oedema test in the rat. Verbascoside administered orally at 150 mg/kg inhibited carrageenan-induced rat paw oedema by 94% after 3 hours ($p < 0.02$), compared to 40% inhibition by indometacin at 10 mg/kg ($p < 0.01$) (Schapoval et al. 1998).

Furthermore, verbascoside was found to have anti-inflammatory effect against D-galactosamin/lipopolysaccharide-induced hepatitis in mice (Xiong et al. 1999).

A study done by Murai et al. (1995) showed that verbascoside had inhibitory effects on arachidonic acid-induced mouse ear oedema. 20 μ l of arachidonic acid (100 mg) dissolved in acetone (1 ml) was delivered to both the inner and outer surfaces of each of the right and left ears of mice. Verbascoside inhibited oedema by 6% at 1 mg/ear, and 14% at 3 mg/ear ($p < 0.05$).

Analgesic activity

Verbascoside (acteoside) exhibited analgesia on acetic acid-induced writhing and on tail pressure pain in mice by the oral administration of 300 mg/kg and 100 mg/kg, respectively. Verbascoside also caused weak sedation by prolongation of pentobarbital-induced anesthesia and on the depression of locomotion enhanced by metamphetamine (Nakamura et al. 1997).

Cardiovascular activity

It has been reported that verbascoside increased perfused rat heart rate (Pennacchio et al. 1999). However, verbascoside (acteoside) administered intravenously to normotensive pentothal anaesthetized rats exhibited a dose-dependent decrease in systolic, diastolic and mean arterial blood pressure; the median effective dose of 10 mg/kg reduced mean arterial blood pressure by 39% for 2-3 minutes, while heart rate also decreased (Ahmad and Rizwani 1995).

Anti-tumour activity

Verbascoside inhibited proliferation of human gastric adenocarcinoma MGC80-3 cell line by 53.2% ($p < 0.001$) at 20 $\mu\text{mol/l}$. When the verbascoside-treated cells were inoculated subcutaneously into BALB/C nude mice, the rate of tumour development decreased by 75% compared to that of animals receiving untreated cells. These effects were thought to be related to antioxidant properties of verbascoside (Li et al. 1997).

II.2.1.2 Assessor's overall conclusions on pharmacology

Mullein flower has been investigated in several pharmacological studies. Both antibacterial and antiviral effects have been showed in *in vitro* studies. The pharmacological activities of certain constituents (aucubin, saponin and verbascoside) *in vivo* may explain some of the effects of mullein flower. However, the data available concerning the pharmacological effects are too limited to draw any conclusions on the effects on common cold.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No information available.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

Due to lack of data, no conclusions can be drawn.

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Acute toxicity

No data found on mullein flower.

Mullein leaf:

Toxicity of mullein leaves (*V. thapsus*) extracts and saponins have been tested in the brine shrimp, and in the radish seed bioassays. Extracts of mullein leaf (*V. Thapsus*) were toxic at higher doses (around 1000 mg/l), whereas the different saponins were toxic at low doses ($LC_{50}=30-40$ mg/l). For aqueous extracts, a decoction was more toxic than an infusion and may contain more toxic compounds than other types of extracts ($LC_{50} < 1000$ mg/l) (Turker and Camper 2002).

There are no data on genotoxicity, carcinogenicity, reproductive and developmental toxicity available on mullein flower.

II.2.3.2 Assessor's overall conclusions on toxicology

No signals of mullein flower having any harmful effects have been identified. Since minimum required data on mutagenicity (Ames test) are not available, inclusion to the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

No data available.

II.3.1.1 Pharmacodynamics

No data available.

Pharmacodynamic interactions

No data available.

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available.

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

Due to lack of data, no conclusions can be made.

II.3.1.2 Pharmacokinetics

No data available.

Pharmacokinetic interactions

No data available.

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

Due to lack of data, no conclusions can be drawn.

II.3.2 Clinical Efficacy³

Mullein flower is used in European, American and Ayurvedic tradition. The traditional use of mullein flower has been thoroughly documented in handbooks.

In addition to being widely used in European tradition, mullein is found abundantly naturalised in the USA (Grieve 1974), and is also mentioned in Ellingwood's American Materia Medica from 1919, where "mulleined" oil (juice extract of the mullein blossoms) is used in the treatment of simple uncomplicated deafness. Both flowers and leaves were at one time official in the U.S.N.F. (Bradley 2006). The use of mullein flower is reported by Nadkarni (1954) in the Indian Materia Medica, and by Chopra et al. (1956) in the Glossary of Indian Medicinal Plants.

³ In case of traditional use the long-standing use and experience should be assessed.

The following indications have been reported for mullein flower:

Mullein preparations were used during the Middle Ages as a remedy for skin and lung disease in cattle and humans. By the end of the nineteenth century, mullein was given in Europe, the UK, and the USA to tuberculosis patients (Blumenthal et al. 2000; Escamilla et al. 2000). Nineteenth century eclectic physicians used mullein for inflammatory diseases of the respiratory and genitourinary tracts and the ear canal (Ellingwood 1983). A sweetened infusion of the mullein flowers strained in order to separate the rough hairs, is considerably used as a domestic remedy in mild catarrhs, colic etc. (Grieve 1974).

Mullein flower is an ingredient of herbal remedies for cough and cold symptoms (Martindale 2007). Mullein flower is employed for treatment of asthma (Chopra et al. 1956), expectorant (Hänsel et al. 1999), and other pulmonary complaints (Chopra et al. 1956; Hänsel et al. 1999). Mullein flower is also used as an infusion to reduce mucus formation and stimulate the coughing up of phlegm (Chevallier 1996).

Bradley (2006) is quoting the information given in *Médicaments à base de plantes: Bouillon blanc, fleur mondée* about indications describing the situation in France:

Oral use

Traditionally used: as adjuvant treatment of the painful component of functional digestive disorders; in the symptomatic treatment of coughs.

Topical use

Traditionally used: as a soothing and antipruriginous local treatment of dermatological ailments, as a topic protector in the treatment of chaps, abrasions or fissures and against insect stings; locally (mouthwash/gargle, pastille) as an analgesic in ailments of the buccal cavity and/or the pharynx; locally in mouthwashes, for buccal hygiene.

Other forms of traditional external uses are mentioned by Bradley (2006). Further references are listed below, but the plant part described is not always obvious. The leaves seem to have been used more than the flowers in topical treatment of inflamed mucosa.

In Germany, the flowers are steeped in olive oil, and the resulting fixed oil is used as a remedy for ear infections and haemorrhoids. (Chevallier 1996). Mullein oil is recommended for earache and discharge from the ear, and for any eczema of the external ear and its canal (Grieve 1974). This oil is said to make an admirable bactericide (Turker and Gurel 2005). An oil produced by macerating mullein flowers in olive oil, stored in a corked bottle during prolonged exposure to the sun, or by keeping it near the fire for several days, is used as a local application in country districts in Germany for piles and other mucus membrane inflammations, and also for frost bite and bruises (Turker and Gurel 2005; Grieve 1974).

Mullein flower is used as a mild expectorant for cold symptoms and coughs (Wichtl 2004), whereby the soothing action of the mucilage (covering the epithelial damage) and the expectorant action of the saponins work together (Wichtl 2004; Weiss 1988). According to Weiss (1988) mullein flower is not so much prescribed for acute catarrhal conditions, and mullein flower is held in reserve for sub-acute states and also chronic bronchitis, when there is still considerable irritation. Demulcent and mild expectorant effects are further explained by Weiss and Fintelmann (2000).

"The flowers of V. densiflorum and V. phlomoides contain a large amount of mucilage as well as acidic saponin and a small quantity of volatile oil. In other words, the mullein is not a pure demulcent, but somewhat of a cross between the demulcents and saponin-bearing expectorants. Mullein flower must be classified as both a demulcent and a mild expectorant. Hence, it is more effective in alleviating subacute diseases and chronic bronchitis with a persistent cough than acute inflammations of the mucous membranes".

The expectorant and antitussive effects of saponins in general are explained by Hostettmann and Marston (1995):

“Saponins possess a general and non-specific ability to produce local irritation, especially of mucous membranes. This can take place in the nasal cavity, the throat, the bronchi, the lungs and in kidney epithelia.”

“The irritation of the throat and respiratory tract probably increases respiratory fluid volume by drawing more water into the bronchial secretions, hence diluting the mucus and reducing its viscosity. Alternatively, the surface activity of the saponins may render the sputum less viscid, making it more mobile and easier to eject. Another possibility is that the amphiphilic nature of saponins causes them to spread out as a monomolecular film at the back of the throat and subsequently aid elimination of mucus.”

A few herbal tea formulas contain mullein flowers as a component (bronchial and cough tea). Some combination preparations, such as cough syrups and cough drops, contain extract of mullein flower among other extracts.

Mullein is believed to have numerous effects and to be valuable in the treatment of wide range of ailments, such as:

Astringent	Tyler 1999; Chopra 1956
Demulcent	Tyler 1999; Chopra 1956; Escamilla et al. 2000;
Tuberculosis	Tyler 1999
Bowel bleeding	Tyler 1999; Chopra 1956
Asthma	Tyler 1999; Nadkarni 1954; Madaus 1938
Hemorrhoids	Tyler 1999; Chopra 1956; Chiej1988
Erysipelas	Tyler 1999; Grieve 1974
Burns	Tyler 1999; Grieve 1974
Ringworm	Grieve 1974
Pectoral	Chopra 1956
Bactericide	Grieve 1974
Diuretic	Bisset and Wichtl 2001
Mouthwash	Bruneton 1995

Evidence regarding the traditional use and posology:

Herbal Medicine, Expanded Commission E Monographs (Blumenthal et al. 2000)

- *Traditional use:* catarrhs of the respiratory tract. Symptomatic treatment of sore throat and cough. Chills, dry coughs, and phlegm congestion due to the mild expectorant action of the saponins
- *Oral dose:* 3-4 g of cut herb for teas and other equivalent galenic preparations for internal use.
 - Infusion; Steep 1.5-2 g of herb in 150-250 ml boiled water for 10 minutes, twice daily. (Note given: More exhaustive extraction of flavonoids if decoction is used; Place 1.5-2 g of herb in 150-250 ml cold water and bring to a boil for 10 minutes, twice daily.)
 - Fluid extract; 1:1 (g/ml): 1.5-2 ml, twice daily.
 - Tincture: 1:5 (g/ml): 7.5-10 ml, twice daily
- *Duration of use:* No information

Herbal Drugs and Phytopharmaceuticals (Wichtl 2004)

- *Traditional use:* Mild expectorant for cold symptoms and coughs. Chills and coughs, etc. Diuretic and anti-rheumatic. Externally for treating wounds.
- *Oral dose:* Tea; Boiling water poured over 1.5-2 g of the finely cut dried mullein flowers (or it is put into cold water and brought to the boil) and after 10-15 minutes passed through a tea strainer (decoction).
- *Duration of use:* No information

Lehrbuch der Biologischen Heilmittel (Madaus 1938)

- *Traditional use*: expectorant, coughs, lung catarrh, asthma, rheumatism, tuberculosis and cramps, externally for treating wounds etc.
- *Oral use*: 1 teaspoon tincture
 - 1 full teaspoon (= 1.1 g) of the flower to cold extract daily
 - For expectorant effect; *V. densiflorum* flowers 30.0. 1 teaspoon *V. densiflorum* in 2 glasses of cold water for 8 hours, before drinking.
- *Duration of use*: No information

Rational Phytotherapy (Schulz et al. 2001)

- *Traditional use*: cough and sore throat
- *Oral dose*: Infusion; 2-3% infusion (3-4 teaspoons/150 ml)
- *Duration of use*: No information

The Complete German Commission E Monographs (Blumenthal et al. 1998)

- *Traditional use*: Catarrhs of the respiratory tract
- *Oral dose*: Unless otherwise prescribed; Daily dose: 3-4 g of herb; equivalent preparations
- *Duration of use*: No information

On this background and the information received from the Member States, the following traditional indication was proposed in the first draft of the assessment report:

Herbal medicinal product traditionally used as an expectorant in cough associated with common cold.

The MLWP stressed in particular the demulcent effect of mucilage, and therefore recommended to alter the indication to:

Herbal medicinal product traditionally used to relieve symptoms of sore throat associated with dry cough and cold.

II.3.2.1 Assessor's overall conclusion on the traditional medicinal use

Traditional medicinal use of mullein flower to relieve symptoms of sore throat associated with dry cough and cold fulfils the requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2001/83/EC as amended.

II.3.2.2 Dose response studies

There are no dose-response studies available.

According to the information about the usage submitted by Germany, a Standard Marketing Authorisation has existed since 1996 for the herbal substance *Verbascum densiflorum* and *Verbascum phlomoides*. It is defined as herbal tea. Daily dosage: 3-4 x a day 1 g drug on 150 ml. This is the same daily dosage described in the German Commission E monograph.

In Blumenthal et al (2000) specifications of solvent are missing, and therefore this preparation cannot be recommended.

The information about Sirupus Verbasci preparations and posology submitted by Poland for decoction is not confirmed in handbooks available to the Rapporteur. As a result, this preparation is not suggested in the monograph.

Based on the listed posology from handbooks (see II.3.2) and posology list from the Member States, the following dosages have been recommended for this indication:

Posology

Herbal substance or herbal preparation for tea preparation (approximately 1.5 -2 g): 3-4 times daily.

Duration of use

Due to the nature of the proposed indications, the use of mullein flower should be limited to 1 week.

According to Wichtl (2004) this is also recommended in the package insert from German Standard Licence (St.Zul.11th Suppl., Published February 1996):

“In acute cases that last longer than one week or periodically reoccur, it is recommended to seek medical advice.”

Likewise, advice about consultation with qualified health care practitioners is included in the monograph.

II.3.2.3 Clinical studies (case studies and clinical trials)

No information available.

II.3.2.4 Clinical studies in special populations (e.g. elderly and children)

None reported.

II.3.2.5 Assessor’s overall conclusions on clinical efficacy

There are no clinical investigations available on mullein flower.

II.3.3 Clinical Safety/Pharmacovigilance

There are no adverse reactions reported from the Member states.

According to De Smet et al. (1993), German Commission E permits the flower of *V. densiflorum* for oral use, and French Guidelines permits peeled flower of *V. densiflorum* for oral use. In the U.S., mullein flower is defined as a dietary supplement and is also generally recognized as safe (GRAS) natural flavouring substance (Wichtl 2004).

II.3.3.1 Patient exposure

None reported.

II.3.3.2 Adverse events

Bibliographic review of safety data of the traditional herbal medicinal substances

The following electronic databases were searched on 24 August 2007 with the search term “Verbascum, Verbasci flos and mullein flower”.

Results:

Scifinder (refined search with the term “adverse”): 3 references obtained (this database covers both chemical abstracts and Medline).

Toxline: 31 references obtained

Pubmed (refined with the term “adverse”): 3 references obtained

Out of these references, no case report of safety concern in connection with mullein flower was identified.

Gordolobo, Spanish for *Verbascum thapsus*, has been reported to cause adverse effects such as cough, distended abdomen (Herbalgram 1994) and dermatitis (Romaguera et al. 1985) in humans. However, it should be mentioned that plants from at least three genera, *Verbascum*, *Gnaphalium*, and *Senecio*, are all given the common Spanish name Gordolobo. These reports on adverse effects are case reports of single patients. Data about dosage, time of use, and other medication are missing, as well, and the diagnosis is not well defined.

The woolly hairs of the plant are sometimes irritant to the skin of sensitive individuals (Felter 1922). The Commission E and the BHC list no known contraindications (Bradley 2006; Blumenthal et al. 2000). However, hypersensitivity to the active substance should be contraindicated.

II.3.3.3 Serious adverse events and deaths

None reported.

II.3.3.4 Laboratory findings

None reported.

II.3.3.5 Safety in special populations and situations

Children (younger than 12 years)

The use of mullein flower is not recommended in children younger than 12 years of age due to lack of available data.

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

None reported.

II.3.3.5.2 Drug interactions

None reported.

II.3.3.5.3 Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use cannot be recommended during pregnancy or breast-feeding.

II.3.3.5.4 Overdose

No case of overdose has been reported.

II.3.3.5.5 Drug abuse

None reported.

II.3.3.5.6 Withdrawal and rebound

None reported.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

Studies have not been performed.

II.3.3.6 Assessor's overall conclusions on clinical safety

There are no adverse reactions reported from the Member States.

Mullein flower has GRAS status in the USA (Wichtl 2004). The Commission E and the BHC list no known contraindications (Blumenthal et al. 2000, Bradley 2006). According to De Smet et al. (1993), German Commission E permits the flower of *V. densiflorum* for oral use, and French Guidelines permit peeled flower of *V. densiflorum* for oral use.

Mullein flower is generally considered as safe. However, due to lack of data, the use of mullein flower cannot be recommended during pregnancy, breast-feeding or in children younger than 12 years of age.

Hypersensitivity or allergy to plants of the *Verbascum* genus should be contraindicated.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Sufficient data are available to develop a Community herbal monograph on the traditional use of mullein flower. Mullein flower is widely used, both in combinations and mono-preparations, according to handbooks and general information. This is also confirmed in the information submitted from Member States.

Traditional medicinal use of mullein flower to relieve symptoms of sore throat associated with dry cough and cold fulfils the requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2001/83/EC as amended.

Mullein flower is generally considered safe under normal conditions of use.

No signals of mullein flower having any harmful effects have been identified. Since minimum required data on mutagenicity (Ames test) are not available, inclusion to the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

Mullein flowers cannot be recommended during pregnancy, breast-feeding or in children younger than 12 years of age.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH

III.2 LITERATURE REFERENCES