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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad) and *V. phlomoides* L., flos

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Verbascum thapsus</i> L., <i>V. densiflorum</i> Bertol. (<i>V. thapsiforme</i> Schrad) and <i>V. phlomoides</i> L., flos
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Herbal substance or comminuted herbal substance as herbal tea for oral use
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Table of contents

Table of contents	2
1. Introduction	4
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof ..	4
1.2. Search and assessment methodology	7
2. Data on medicinal use	8
2.1. Information about products on the market	8
2.1.1. Information about products on the market in the EU/EEA Member States	8
2.1.2. Information on products on the market outside the EU/EEA	9
2.2. Information on documented medicinal use and historical data from literature	10
2.3. Overall conclusions on medicinal use	12
3. Non-Clinical Data	13
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	13
3.1.1. Primary pharmacodynamics	13
3.1.2. Secondary pharmacodynamics	13
3.1.3. Safety pharmacology	15
3.1.4. Pharmacodynamic interactions	16
3.1.5. Conclusions	16
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof.....	16
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof	16
3.3.1. Single dose toxicity.....	16
3.3.2. Repeat dose toxicity.....	16
3.3.3. Genotoxicity	16
3.3.4. Carcinogenicity.....	16
3.3.5. Reproductive and developmental toxicity	16
3.3.6. Local tolerance	16
3.3.7. Other special studies.....	16
3.3.8. Conclusions	17
3.4. Overall conclusions on non-clinical data	17
4. Clinical Data	17
4.1. Clinical pharmacology	17
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	17
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	17
4.2. Clinical efficacy	17
4.2.1. Dose response studies.....	17
4.2.2. Clinical studies (case studies and clinical trials)	17
4.3. Clinical studies in special populations (e.g. elderly and children)	18
4.4. Overall conclusions on clinical pharmacology and efficacy.....	18

5. Clinical Safety/Pharmacovigilance	18
5.1. Overview of toxicological/safety data from clinical trials in humans.....	18
5.2. Patient exposure	18
5.3. Adverse events, serious adverse events and deaths.....	18
5.4. Laboratory findings.....	18
5.5. Safety in special populations and situations	18
5.5.1. Use in children and adolescents.....	18
5.5.2. Contraindications.....	18
5.5.3. Special Warnings and precautions for use	19
5.5.4. Drug interactions and other forms of interaction.....	19
5.5.5. Fertility, pregnancy and lactation.....	19
5.5.6. Overdose.....	19
5.5.7. Ability to drive or operate machinery or impairment of mental ability	19
5.5.8. Safety in other special situations	19
5.6. Overall conclusions on clinical safety.....	19
6. Overall conclusions (benefit-risk assessment)	19
Annex	20

1. Introduction

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

- 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., ref.: 1853).

German pharmacopoeial grade mullein flower must have a swelling index of not less than 9 and it must not contain more than 5% calices and discoloured flowers (brown corollas) (Blumenthal, 2000). The Swiss pharmacopoeia requires a swelling index of not less than 12 (Blumenthal, 2000). The European Pharmacopoeia 9.4 includes a test for swelling index with minimum 9.

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.

- Herbal preparation(s)

Comminuted herbal substance.

- 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.

This assessment report includes data regarding monopreparations containing mullein flower and herbal preparations from this herbal substance. Literature regarding combination products is not part of the assessment.

Vitamin(s): Not applicable

Constituents:

Iridoid glycosides:	0.56% in <i>V. phlomoides</i> , 0.13% in <i>V. densiflorum</i> , including aucubin, catalpol, 6-xylosylaucubin and 6-xylosylcatalpol. <i>V. densiflorum</i> flower contains 10-fold less aucubin but 2-fold more catalpol than <i>V. phlomoides</i> flower (Bradley 2006). Also, 6-(4"-p-coumaroyl)-xylosylaucubin (named phlomoide) and another iridoidester glycoside, specioside, occur in <i>V. phlomoides</i> flower (Bradley 2006).
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<p>Flavonoids:</p>	<p>0.57% in <i>V. phlomoides</i>, 0.22% in <i>V. densiflorum</i>, although up to 4% of flavonoids has been claimed (Bradley 2006).</p> <p>In the flower of <i>Verbascum thapsus ssp. thapsus</i>: 6-hydroxyluteolin 7-glucoside, 3'-methylquercetin and 7,4'-dihydroxyflavone 4'-rhamnoside (Bradley 2006).</p> <p>In <i>V. densiflorum</i> 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).</p> <p>In <i>V. phlomoides</i> 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).</p> <p>Quercetin (17.29 mg/g) (Grigore <i>et al.</i>, 2013)</p>
<p>Phenylethanoid glycosides:</p>	<p>Verbascoside (acteoside), ca. 0.6% in <i>V. densiflorum</i> flower, but only traces in <i>V. phlomoides</i> flower, traces of forsythoside B (verbascoside 6'-apioside) in both species (Bradley 2006).</p>
<p>Triterpene saponins:</p>	<p>Verbascosaponin, a monodesmosidic oleanane saponin with an ether bridge between C13 and C28 and a group of four neutral sugar residues at the 3-position, was first isolated in 1980 from <i>V. phlomoides</i> flower; The structure was revised in 1992. The closely-related verbascosaponin A, verbascosaponin B and desrhamnosyl verbascosaponin have also been isolated from <i>V. phlomoides</i> (Bradley 2006).</p> <p>In <i>Verbascum thapsus</i> flower: four saponins of fairly similar structure have been isolated and named thapsuins A and B, and hydroxythapsuins A and B (Bradley 2006).</p> <p>In <i>V. densiflorum</i> flower: No saponins have been confirmed in <i>V. densiflorum</i> flowers (Bradley 2006). Hagers Handbuch has given a value for the saponin content in flowers of <i>V. phlomoides</i> of 0.007% (Blaschek <i>et al.</i>, 2006). This number is based on an article by Tschesche <i>et al.</i>, 1980. This is not a chemical analytical article, and the saponin determination described has limitations, e.g. it is</p>

	<p>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 <i>in vitro</i>. 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 X 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.</p>
Polyphenols:	<p>Total polyphenols are expressed as gallic acid (4.18%)</p> <p>It was also shown by HPLC that polyphenolcarboxylic acids such as ferulic, caffeic and rosmarinic acids are found in significant amount (29.61, 39.96, and 14.93 mg/g respectively) according to Grigore <i>et al.</i>, 2013.</p>
Polysaccharides:	<p>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 (<i>V. phlomoides</i> and/or <i>V. densiflorum</i>) (Bradley, 2006).</p>
Other constituents:	<p>Phytosterols (β-sitosterol and ergosterol peroxide) and oleanolic acid in <i>Verbascum thapsus</i> flower; phytosterol glycosides and digiprolactone (a bicyclic</p>

	monoterpene) in <i>V. phlomoides</i> flower, fixed oil in flowers of <i>V. phlomoides</i> (2.4%) and <i>V. densiflorum</i> (1.6%), in which the main fatty acids are palmitic and linolenic acids; amino acids and free sugars in <i>V. densiflorum</i> flower; carotenoids and xanthophylls (Bradley 2006).
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1.2. Search and assessment methodology

This report is based on a scientific review of the scientific and traditional literature referring to *Verbascum thapsus* L. The following electronic databases were searched in November 2016 and 2017 with these search terms:

Scientific databases: SciFinder

Verbascum thapsus: 6

Verbascum densiflorum: 3

Verbascum phlomoides: 71

Verbasci flos: 1 references

Mullein flower: 0

Verbascum thapsus flos: 0

Medical databases: The Cochrane Library

Verbascum thapsus: 6

Verbasci flos: 1 references

Mullein flower: 0

Verbascum thapsus flos: 0

PubMed:

Verbasci flos: 4 references

Verbascum thapsus: 163

Verbascum densiflorum: 6

Verbascum phlomoides: 163

Other resources: *European Scientific Cooperative on Phytotherapy. ESCOP Monograph. The Scientific Foundation for Herbal Medicinal Products. E/S/C/O/P Online Series, 2014: Verbasci Flos Mullein flower: 38 articles*

Toxicological databases: Toxline

Verbascum thapsus: 6

Verbasci flos: 1 references

Mullein flower: 0

Verbascum thapsus flos: 0

Pharmacovigilance resources:

The World Health Organisation's Uppsala Monitoring Centre (WHO-UMC): 1 case report

Search performed on 09.11.2016 for *Verbascum thapsus*, mullein and mullein extract (synonym for *Verbascum* spp.). An updated search was performed on 01.11.2017 for *Verbascum densiflorum* and *Verbascum phlomoides*.

Data from EU and non-EU regulatory authorities: for information about products on the market in the EU/EEA Member States, see table 1 in section 2.1.1.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
Verbasci flos extractum fluidum (DER 0.5-1:1), extraction solvent ethanol 40% (V/V)	Traditional herbal medicinal product used for sore throat accompanying the dry cough and cold	Syrup 15 g of extract in 100 g of product. Adolescents and adults: 5 ml, 3-4 times daily or 10 ml two times daily. Not use longer than 1 week	10.2001 MA*; 03.2011 TUR, PL
Verbasci flos extractum fluidum DER (1:5), extraction solvent ethanol 60% V/V.	Traditional herbal medicinal product used for sore throat accompanying the dry cough and cold	Syrup 15 g of extract in 100 g of product. Adolescents and adults: 15 ml, 3-4 times a day. Not use longer than 1 week	12.2008, TUR, PL
Dried herbal substance	Traditional herbal medicinal product used for sore throat accompanying the dry cough and cold	Herbal tea Infusion of 1 g of herbal substance in 150 ml of boiling water. Infuse, under cover 10-15 min., strain. Drink a warm infusion 3-4 times a day.	03.1995, MA*, PL
Dried herbal substance	Traditional herbal medicinal product used for sore throat accompanying the dry cough and cold	Herbal tea Infusion of 1 g substance in 150 ml of boiling water. Infuse, under cover 10-15 min., strain. Drink a warm infusion 3-4 times a day	12.2000, MA*, PL
Dried herbal substance	Cough and cold	Herbal tea > 12 years: For drinking: 1 g/150 ml boiling water	1996, MA, DE

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory Status
		3-4 times daily If the symptoms persist longer than a week or in case of recurrent symptoms, a doctor should be consulted.	

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

*Authorisation according to national law in Poland.

Information on relevant combination medicinal products marketed in the EU/EEA

Combination products containing mullein flower are and have been marketed in Europe historically as shown in the market overviews published in the first assessment of mullein flower. Belgium has had a tea with mullein leaves and flowers since 1964, Germany has had 10 combinations since 1978. Combination products are available in Slovenia since 1993 and Denmark had a well-established combination product on the market between 1997-2000. Both Czech Republic and Slovakia have had combination products since 1969. This combination that was on the market both in Slovakia and in Czech Republic is an example:

Czech Republic

Species pectorals Planta

Herbal tea for oral use containing Plantaginis folium 23 g, Althaeae radix 22 g, Farfarae folium 22 g, Menthae piperitae herba 10 g, Liquiritiae radix 10 g, Verbasci flos 8 g and Foeniculi fructus 5 g in 100 g of the mixture

Indication: As an adjuvant for treatment of acute and chronic upper respiratory tract catarrhs

Posology: 1 spoon/250 ml of boiling water 3 times daily. On the market since 1969, switched to TU in 2011

Slovakia

Species pectorals Planta

Herbal tea containing Plantaginis folium 23 g (Ribwort plantain leaf), Althaeae radix 22 g (Marshmallow root), Farfarae folium 22 g (Coltsfoot leaf), Menthae piperitae herba 10 g (Peppermint herb), Liquiritiae radix 10 g (Licorice root), Verbasci flos 8 g (Mullein flower), Foeniculi fructus 5 g (Fennel seed) in 100 g of herbal mixture.

Indication: Subsidiary medicine for upper respiratory tract ailments and coughs. It alleviates phlegm, dissolves and eases mucus. The infusion can also be used for gargling.

Posology: Pour 1 cup of boiling water (250 ml) over 1 spoon of herbal mixture and steep in a covered cup for approximately 15 minutes. Do not boil. Can be sweetened with honey. Drink freshly prepared, 3 times daily. On the market since 30.12.1969.

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

Not applicable

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

The use of mullein flower has been continuously documented in handbooks, pharmacopoeias and scientific literature. 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. 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 (Bradley, 2006). The Dispensatory of the United States of America (1918), 20th edition by Remington JP and Woods HC, editors, gives an elaborate description of the "the dried corollas, with adhering stamens", of *Verbascum phlomoides* L. or of *Verbascum thapsiforme* Schrad. (Fam. Scrophulariaceae) and states that Mullein Flowers (Verbasci Flores) are official.

Both 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).

The British Herbal Pharmacopoeia (BHP) 1983 monograph was 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 utilised as piscicide (Wilhelm, 1974). The following traditional uses and posologies have been recorded for mullein flower (see table 2).

Table 2: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Posology Duration of use	Reference
Dried herbal substance	Expectorant, disinfectant and coating mucous membranes	Infusion 10% Drink one glass - two times a day	Roeske, 1955
Dried herbal substance	Mild expectorant, disinfectant, mucilaginosum	Herbal tea 1 tablespoon in a glass of water as decoction	Receptariusz Zielarski (Gobiec, 1967)
Dried herbal substance	External use on wounds, burns and bedsores	Herbal tea 1 tablespoon in a glass of water as decoction	Receptariusz Zielarski (Gobiec, 1967)
Comminuted	Catarrhs of the	Infusion	Herbal Medicine,

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Posology Duration of use	Reference
herbal substance	respiratory tract. Symptomatic treatment of sore throat and cough Chills, dry coughs, and phlegm congestion	Steep 1.5-2 g of herbal substance 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 herbal substance in 150-250 ml cold water and bring to a boil for 10 minutes, twice daily.)	Expanded Commission E Monographs (Blumenthal <i>et al.</i> , 2000)
Fluid extract: 1:1 (g/ml)	Catarrhs of the respiratory tract. Symptomatic treatment of sore throat and cough Chills, dry coughs, and phlegm congestion	1.5-2 ml, twice daily.	Herbal Medicine, Expanded Commission E Monographs (Blumenthal <i>et al.</i> , 2000)
Tincture: 1:5 (g/ml)		7.5-10 ml, twice daily	
Comminuted herbal substance	Mild expectorant for cold symptoms and coughs. Chills and coughs, etc. Diuretic and anti-rheumatic. Externally for treating wounds	Herbal tea Boiling water poured over 1.5-2 g of the finely cut dried mullein flowers. Steep for 10-15 min and strain	Teedrogen (Wichtl 1 st ed. 1984, 2 nd ed. 1989)
Comminuted herbal substance	Catarrhs of the respiratory tract	Mode of administration: Cut dried herb for tea infusions as well as other galenical preparations for internal use. Unless otherwise prescribed: daily dosage 3-4 g of dried mullein flowers or corresponding preparations.	German Commission E monograph (Mullein flower, Published February 1, 1990) cited in Wichtl (2001)
Comminuted herbal substance	For expectorant effect	1 teaspoon (1.1 g) in 2 glasses of cold water for 8 hours, before drinking during the day.	Lehrbuch der Biologischen Heilmittel, Band III. Georg Thieme Verlag, Leipzig: 2789 (Madaus,

Herbal preparation	Documented use / Traditional use	Pharmaceutical form Posology Duration of use	Reference
			1938)

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance	Mild expectorant for cold symptoms and coughs. Chills and coughs, etc.	Herbal tea Boiling water poured over 1.5-2 g of the finely cut dried mullein flowers. Steep for 10-15 min and strain	Teedrogen (Wichtl 1 st ed. 1984, 2 nd ed. 1989)

In the first version of the monograph, published in 2008, it was concluded that the traditional use of mullein flower in cough and cold is in particular as a demulcent, and therefore the phrasing of the indication reflect the "the traditional use to relieve symptoms of sore throat associated with dry cough and cold".

No new references of relevance for the traditional use have been included during the revision. Taking into account the information received from the member states and historical data from literature, the conclusions on indication and posology (including the herbal substance and the dosage frequency, i.e. 3-4 times daily) from the first version of the monograph are retained.

The phytotherapeutic traditional use of mullein flower as a diuretic and diaphoretic is regarded as beneficial pharmacological effects in common cold. However, these effects are not appropriate therapeutic indications. As no complete information about the posology is available, the external use for treating wounds is not included in the monograph.

The traditional medicinal use of mullein flower is considered fulfilled in accordance with the requirement of medicinal use for at least 30 years (15 years within the European Union) in Directive 2004/24/EC.

The following traditional use indication is included in the monograph:

"Traditional herbal medicinal product used to relieve symptoms of sore throat associated with dry cough and cold.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use."

The following posology is included in the monograph for the herbal substance and herbal preparation:

Adolescents, adults and elderly

Single dose:

Herbal tea: 1.5-2 g of the herbal substance or comminuted herbal substance in 150 ml boiling water as a herbal infusion three to four times daily.

Daily dose: 4.5-8 g

Duration of use

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Method of administration

Oral use

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

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 1.38-fold for the commercial tea combination of coltsfoot, fennel, anise, plantain, liquorice, fenugreek, marshmallow root, and thyme . The different components of the cough tea had different effects on the mucociliar 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).

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3.1.2. Secondary pharmacodynamics

Antibacterial activity

A study done by Turker and Camper (2002) showed that mullein flower oil (*Verbascum thapsus* flowers extracted 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 lyophilised infusion from *V. densiflorum* flower exhibited antiviral activity against several influenza A strains, an influenza B strain and fowl plague virus (Zgórniak-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 (Zgórniak-Nowosielska *et al.*, 1991).

An earlier study also demonstrated antiviral activity of mullein flower (*Verbascum 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.

Antitumour activity

The mullein flower oil (*Verbascum thapsus* flowers extracted in pure olive oil) showed antitumour 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).

Pharmacological activities of isolated 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 *in vitro*

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).

Anti-inflammatory activity *in vivo*

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 *in vivo*

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 *in vitro* and *in vivo*

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 mM reduced (6.3–62.3%) nitrite accumulation in lipopolysaccharide (0.1 µg/ml) stimulated J774.1 cells. At 200 mM, they inhibited by 32.2–72.4% nitrite accumulation induced by lipopolysaccharide (0.1 µg/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).

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 µl 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 ($p < 0.05$).

Cardiovascular activity *in vitro* and *in vivo*

In isolated, perfused rat hearts (Langendorff model) verbascoside (1 mM) 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 coronary perfusion rate ($p = 0.016$) when tested against the competitive α -adrenergic blocker phentolamine (1 µM) (Pennacchio *et al.*, 1999).

It has been reported that verbascoside increased perfused rat heart rate (Pennacchio *et al.*, 1999). However, verbascoside (acteoside) administered intravenously to normotensive pentothal anaesthetised 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).

Analgesic activity *in vivo*

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

Antitumour activity *in vivo*

Verbascoside inhibited proliferation of human gastric adenocarcinoma MGc80-3 cell line by 53.2% ($p < 0.001$) at 20 µmol/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).

3.1.3. Safety pharmacology

No information found.

3.1.4. Pharmacodynamic interactions

No information found.

3.1.5. Conclusions

Mullein flower and some of its constituents have been investigated in preclinical studies. Results from relevant experimental studies that support the proposed indications are limited.

None of the reported pharmacological studies constitute any cause for safety concern.

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

No data are found on pharmacokinetics.

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

3.3.1. Single dose toxicity

No data found.

3.3.2. Repeat dose toxicity

No data found.

3.3.3. Genotoxicity

No data found on genotoxicity for mullein flower.

Verbascoside significantly ($p < 0.05$) reduced cell viability at 0.01-1 mM and mitotic index at 0.005-0.1 mM in mitogen-stimulated human lymphocytes. It induced a significant and concentration related increase of chromosome aberrations, an increase in the percentage of aberrant cells ($p < 0.01$) and in sister chromatid exchanges (Santoro *et al.*, 2008).

3.3.4. Carcinogenicity

No data found.

3.3.5. Reproductive and developmental toxicity

No data found.

3.3.6. Local tolerance

No data found.

3.3.7. Other special studies

No data found.

3.3.8. Conclusions

Non-clinical information on the safety of mullein flower is scarce.

Tests on reproductive toxicity, genotoxicity and carcinogenicity on mullein flower have not been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on mullein flower to support the proposed indications are very limited. None of the reported pharmacological studies constitute any cause for safety concern.

Specific data on pharmacokinetics and interactions are not found.

Non-clinical information on the safety of mullein flower is scarce.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Oral administration of mullein flower can be regarded as safe at traditionally used doses.

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

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

4. Clinical Data

4.1. Clinical pharmacology

No data found.

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

No data found.

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

No data found.

4.2. Clinical efficacy

No data found.

4.2.1. Dose response studies

No data found.

4.2.2. Clinical studies (case studies and clinical trials)

No data found.

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

No data found.

4.4. Overall conclusions on clinical pharmacology and efficacy

There are no data on clinical pharmacology or efficacy found for mullein flower.

5. Clinical Safety/Pharmacovigilance

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

No data found regarding the herbal substance.

5.2. Patient exposure

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

No special risks have been identified.

5.3. Adverse events, serious adverse events and deaths

In the Vigilize database of the World Health Organization's Uppsala Monitoring Centre for the period up to November 2017, there was one spontaneous report of suspected adverse drug reactions associated with the single-ingredient *Verbascum thapsus*, mullein and mullein extract (synonym for *Verbascum* spp.) reporting on hepatitis. Two other spontaneous reports included a combination of several herbs and medicinal products including reactions in other organ systems (allergy, CNS).

Assessor's comment: There are not sufficient safety data to include any undesirable effects in section 4.8 in the monograph.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

No data found.

The oral use of mullein flower is not recommended in children due to the lack of adequate data. There are no studies in adolescents between 12 and 18 years available. The recommended dosage for oral use in adults and adolescents is supported by use in member states.

5.5.2. Contraindications

No data found. However, for safety reasons the use is contraindicated in persons with hypersensitivity to the active substance.

5.5.3. Special Warnings and precautions for use

Patients using the product should consult a doctor or a qualified health care practitioner if dyspnoea, fever or purulent sputum occurs.

5.5.4. Drug interactions and other forms of interaction

No data found.

5.5.5. Fertility, pregnancy and lactation

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

5.5.6. Overdose

No cases of overdose from mullein flower have been reported.

5.5.7. Ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been found.

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

Mullein flower can be recognised as safe when used in recommended dosages under specified conditions.

6. Overall conclusions (benefit-risk assessment)

No new data of relevance for changes in the content of the monograph were found during the revision.

There are sufficient data available to support a European Union monograph on the traditional use of mullein flower. Traditional use has shown that mullein flower can be recognised as safe when used in recommended dosages under the conditions specified in the monograph.

There are no clinical data available. The criteria required for "well-established medicinal use according to Directive 2001/83/EC is not fulfilled.

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

Traditional medicinal use of mullein flower has been found to fulfil the requirement of medicinal use for at least 30 years (15 years within the European Union) according to Directive 2004/24/EC for the following indication:

"Traditional herbal medicinal product used to relieve symptoms of sore throat associated with dry cough and cold.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use."

Due to the lack of sufficient safety data the use of mullein flower cannot be recommended during pregnancy and lactation.

As no safety data from the use in children are available, the use of mullein flower is not recommended in children under 12 years of age. However, based on the long-standing medicinal use, as well as the absence of reports of serious adverse events, a sufficient degree of safety as necessary for traditional herbal medicinal products can be assumed for adolescents (over 12 years of age).

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Annex

List of references