EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2012
EMA/HMPC/113577/2012
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Primula veris* L. and/or *Primula elatior* (L.) Hill, radix

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Primula veris* L., *Primula elatior* (L.) Hill, radix
Herbal preparation(s)	A) Dry extract (DER 3-9:1), extraction solvent ethanol 40-50% v/v B) Liquid extract (DER 1:1), extraction solvent ethanol 70% v/v C) Liquid extract (DER 1:2.0-2.5), extraction solvent ethanol 70% v/v D) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 70% v/v E) Soft extract (DER 5-10:1), extraction solvent water F) Soft extract (DER 1-4:1), extraction solvent ethanol 20-55% v/v G) Soft extract (DER 6-10:1), extraction solvent methanol, water, ammonia solution 10% (50.0:49.5:0.5) H) Soft extract (DER 6-10:1), extraction solvent methanol 50% I) Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Other herbal preparations in liquid and solid dosage forms for oral use.
Rapporteur	R. Länger
Assessor(s)	R. Länger

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

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

- Herbal substance(s)

Primula root (Primulae radix) consists of the whole or cut, dried rhizome and root of *Primula veris* L. or *Primula elatior* (L.) Hill as described in the European Pharmacopoeia (European Pharmacopoeia 2008).

Constituents (Hänsel *et al.* 1994, Wichtl 2004, Hänsel & Sticher 2007, Tschesche & Ballhorn 1975, Tschesche *et al.* 1983):

The characteristic constituents are triterpene saponins (usually 3 – 10 [-12]%) and phenolic glycosides. The triterpene saponins are of the oleanane-type with branched sugar chains at the hydroxyl-group at the C-3.

Saponins from *Primula elatior* are derived from the aglycone protoprimulagenin A, which is converted during acid hydrolysis to the artefact primulagenin A. The main saponin is called primulasaponin, it is characterised by a sugar chain consisting of glucuronic acid (Glu), glucose (Glc), galactose (Gal) and rhamnose (Rha). Minor saponins differ in the sugar chain (Hänsel & Sticher 2007).

Main aglycones from the saponins of *Primula veris* are anagalligenin, priverogenin B and priverogenin B-22-acetate, important saponins are primacrosaponin (which has been isolated from *Primula veris* subsp. macrocalyx, Calis *et al.* 1992) and priverosaponin B.

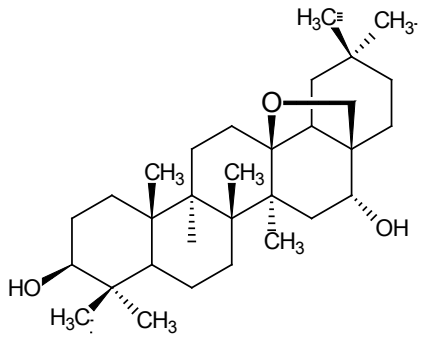
The haemolytic index (HI) has been used for biological standardisation of saponin containing herbal substances and herbal preparations. Although no longer in use the HI facilitates a comparison between the HI of a herbal substance and preparations thereof and allows an estimation of the saponin content. The HI of Primulae radix was defined in the Austrian Pharmacopoeia (ÖAB 9) with 3000.

The phenolic glycosides primverin and primulaverin occur in both species in very variable amounts up to 2.3%, they are 2-primeverosides of 4-methoxy- and 5-methoxysalicilyc acid methyl esters (Thieme & Winkler 1971). These substances change during drying into the odoriferous aglycones (Wichtl 2004).

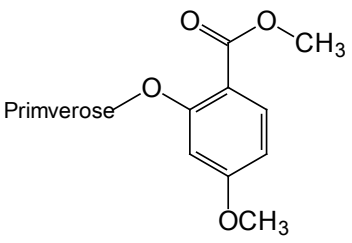
Characteristic sugars of the underground organs are primverose (2-ß-(6-ß-Xylosido)-glucose, Hänsel & Sticher (2007) and the heptitol volemitol (= primulitol, Hegnauer 1969).

The underground organs do not contain primin or other quinoid compounds, which are responsible for contact allergenic properties of aerial parts of species of the genus Primula (Hausen 1978).

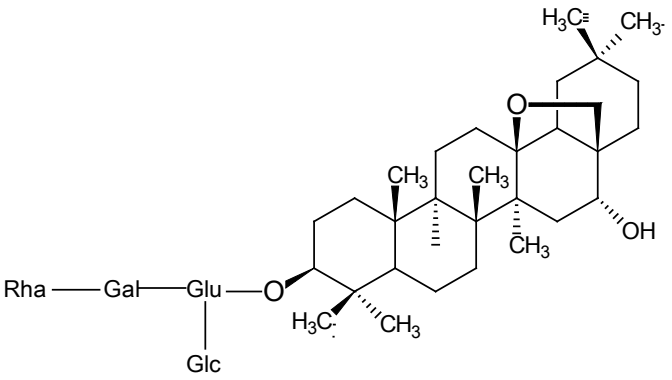
An overview on the chemical structures of important constituents is given in figure 1.



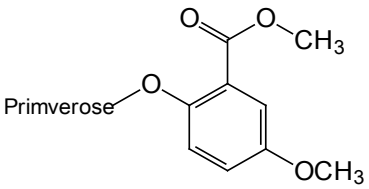
Protoprimulagenin A



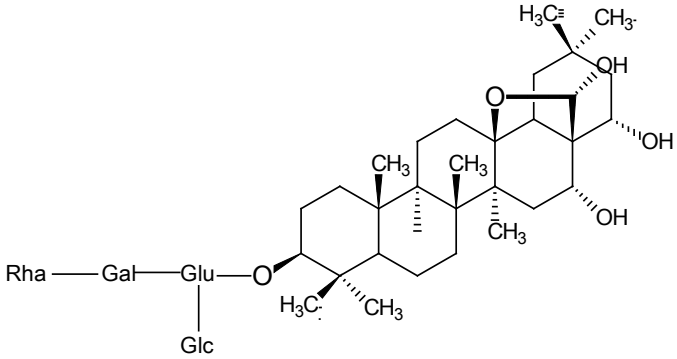
Primulaverin



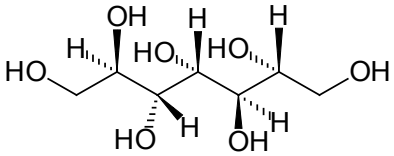
Primulasaponin



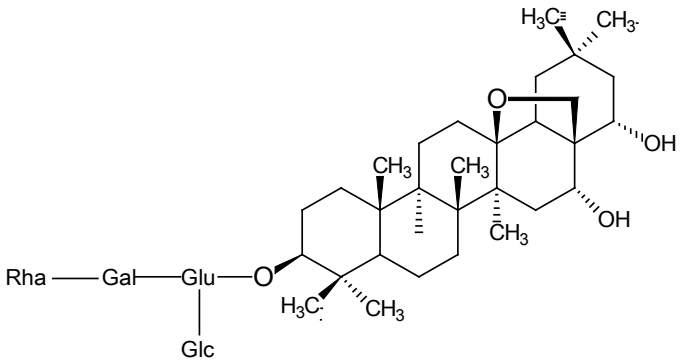
Primverin



Primacrosaponin with the aglycone anagalligenin



Volemitol



Priverosaponin B with the aglycone priverogenin

Figure 1: Chemical structures of important constituents of Primula root.

- Herbal preparation(s)

Herbal preparations with evidence of traditional use:

A) Dry extract (3-9:1), extraction solvent ethanol 40-50% v/v; in the Austrian Pharmacopoeia (ÖAB) at least since 1960 a dry extract with a DER of 3-3.5:1 is included, the HI is specified with 9,000 – 11,000 (corresponding to a saponin content of approximately 25%).

B) Liquid extract (1:1), extraction solvent ethanol 70% (m/m): in the Austrian Pharmacopoeia at least since 1960. HI 2,700 – 3,300 (corresponding to a saponin content of approximately 7.5%).

C) Liquid extract (1:2.0-2.5), extraction solvent ethanol 70% v/v. Mentioned in handbooks of phytotherapy at least since 30 years.

D) Tincture (1:5), extraction solvent ethanol 70% v/v; the tincture in the ÖAB is specified at least since 1960 with a HI of 490 – 600 (corresponding to a saponin content of approximately 1.36%).

E) Soft extract (5-10:1), extraction solvent water: medicinal product on the market in Germany at least since 30 years.

F) Soft extract (1-4:1), extraction solvent ethanol 20-55% v/v: medicinal product on the market in Germany at least since 30 years.

G) Soft extract (6-10:1), extraction solvent methanol, water, ammonia solution 10% (50.0:49.5:0.5): medicinal product on the market in Germany at least since 30 years.

H) Soft extract (6-10:1), extraction solvent methanol 50%: medicinal product on the market in Germany at least since 30 years.

I) Comminuted herbal substance for preparation of a herbal tea.

The preparation has to be specified for the individual finished product.

- 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.

Primula root extracts are used in combinations with many other herbal substances/herbal preparations, in particular the combination with thyme is widespread.

This monograph refers exclusively to Primula root. Data from combination products are considered for the assessment of safety, but not for the evaluation of efficacy of Primula root as the only active ingredient.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations Standard marketing authorisation
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

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

1.3. Search and assessment methodology

MedLine, Scopus: accessed October 2006; for the systematic review/revision: December 2011.

Libraries specialised in pharmaceutical literature (e.g. Pharmacy and Nutritional Sciences library, University of Vienna)

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The underground organs of *Primula veris* and *Primula elatior* have been introduced into the European phytotherapy after World War I as a substitute of Senegae radix (Joachimowitz 1920 cited in Auster & Schäfer 1961, Gaisböck 1924, Wiesner 1928). Since these days the herbal substance (due to the size of the underground parts only in comminuted form) as well as several herbal preparations are in medicinal use. For the above-mentioned herbal preparations, the evidence for at least 30 years of medicinal use including at least 15 years in the EU could be verified. Therefore for the comminuted Primula root and the other mentioned preparations, the qualification as a traditional herbal medicinal product is fulfilled.

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

The following indications have been reported for Primula root:

Respiratory, thoracic and mediastinal disorders

Productive cough	Antonone *et al.* 1988, Steinegger & Hänsel 1992, ESCOP monograph 2003, Wichtl 2004
Catarrhs of respiratory tract	Steinegger & Hänsel 1992, Hänsel *et al.* 1994, German Commission E (cited in Blumenthal *et al*. 1998), ESCOP monograph 2003, Wichtl 2004
(Chronic) bronchitis	Wichtl & Neubeck 2006, Steinegger & Hänsel 1992, ESCOP monograph 2003, Weiß 1991, Wichtl 2004
Obstructed phlegm in the broncho-pulmonary system	Wichtl 2004
Folk medicine: whooping cough, asthma	Wichtl 2004

Further indications

Madaus (1938) summarises that Primula (plant part not mentioned) influences positively rheumatic complaints and the disposition to gout. He also recommends Primula for migraine and nervous headache. Furthermore, a diuretic effect is described (Hänsel *et al.* 1994, Fournier 1948). It is also reported that the external application of infusions should enhance the absorption of haematomas (Flamm *et al.* 1940).

Based on the available literature and the known actions of saponins, the following text on the indication is recommended:

"Traditional herbal medicinal product used as an expectorant in cough associated with cold. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use."

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

Primula root extracts are usually used in combination with other herbal substances. The content of Primula root in these preparations varies from 18 to 60 mg in tablets and from 400 mg/100 g to 5 g/100 g in liquid preparations.

Posology in adults

Comminuted herbal substance

Reference	**Recommendation for preparation**	**Recommended daily dose**
Wichtl 2004	0.2 - 0.5 g (place in cold water, heat to boiling, wait 5 minutes), every 2-3 hours	0.6 - 3 g
DAB 10 commentary		0.5 - 1.5 g
ÖAB 9	0.2 g per cup	0.6 g
Pharm. Française, Xème	decoction 2-3%	
Ergänzungsbuch 6 1941	single dose 0.5 g (= 30 g decoction 1.5%)	1.5 g
List & Hörhammer 1977	single dose 0.5 g	1.5 g
Hänsel *et al.* 1994		1 g
ESCOP 2003		0.5 - 1.5 g (in France also up to 10 g)
Auster & Schäfer 1961	single dose 0.5 g as decoction (0.5%)	1.5 g
Madaus 1938	1 cup of decoction (3:100) 3 times daily	up to 10 g
Weiß 1991	in herbal teas up to 40% ¼ of a teaspoon (= 0.87 g) per cup of decoction, every 2-3 hours	up to 6 g
Commission E		0.5 - 1.5 g
Fournier 1948	*decoction with 20 - 30 g per litre as a **diuretic** = 2.5 g per 150 ml; 3 times daily*	*7.5 g*

1 teaspoon = approximately 3.5 g

Herbal preparations

	Single dose	**Daily dose**
A) Dry extract:		
ÖAB 2008	0.1 - 0.2 g	0.3 - 0.6 g
Pharm. Française Xème		0.2 - 0.5 g
B) Liquid extract		
ÖAB 2008	0.5 g	1.5 g
C) Liquid extract		

Hänsel 1994	0.5 g	1.5 g
Weiß 1991	20 drops (0.6 g)	2.4 g
D) Tincture		
DAB 10 commentary		1.5 - 3 g
ÖAB 2008	0.5 - 1 g	1.5 - 3 g
DAB 9 commentary	0.3 - 1 ml	1 - 3 ml
Hänsel 1994	0.5 - 1 g	1.5 - 3 g
Ergänzungsband 6	2.5 g	7.5 g
Commission E		1.5 - 3 g
Auster & Schäfer 1961	2.5 g	7.5 g
Weiß 1991	20 drops	2.5 g
G) Soft extract		
Information from the German authorities	22.5 mg	67.5 mg

Posology in adolescents

See below data given by Dorsch *et al.* 2002 and those published by ESCOP 2003.

Proposed posology

Based on these references, the following posology is recommended for adolescents over 12 years of age, adults and elderly:

	Single dose	**Daily dose**
Comminuted herbal substance	0.2 - 0.5 g	0.5 - 1.5 g
A) Dry extract (according to Austrian Pharmacopoeia with DER 3-3.5:1)	0.1 - 0.2 g	0.3 - 0.6 g
A) Dry extract (different DER to Austrian Pharmacopoeia)	equivalent to 0.2 - 0.5 g herbal substance (depending on the actual DER)	equivalent to 0.5 - 1.5 g herbal substance (depending on the actual DER)
B) Liquid extract	0.5 g	1.5 g
C) Liquid extract	0.6 g	1.5 g
D) Tincture	0.5 – 1 g	2.4 g
E) Soft extract	equivalent to 0.2 - 0.5 g herbal substance (depending on the actual DER)	equivalent to 0.5 - 1.5 g herbal substance (depending on the actual DER)
F) Soft extract	equivalent to 0.2 - 0.5 g herbal substance (depending on the actual DER)	equivalent to 0.5 - 1.5 g herbal substance (depending on the actual DER)
G) Soft extract	22.5 mg	67.5 mg
H) Soft extract	equivalent to 0.2 - 0.5 g herbal substance (depending on the actual DER)	equivalent to 0.5 - 1.5 g herbal substance (depending on the actual DER)

Dosage frequency: May be taken every 2 to 3 hours (up to 3 times daily)

Posology in children

The data given by Dorsch *et al.* 2002 may be questioned since they are coming from a German publication where the doses were calculated without real clinical data. In part II of the same publication empirical data were collected from 500 paediatricians via a questionnaire which e.g. did not ask for the kind of preparation and for adverse events. The data published by ESCOP 2003 refer to Dorsch *et al.* 2002.

Age group	**Dosage recommendation, daily dose (calculated as Primula root)**	**References**
Under 1 year	0.05 – 0.3 g	Dorsch *et al.* 2002
1 – 4 years	0.2 – 0.6 g	Dorsch *et al.* 2002
4 – 10 years	0.5 – 1.0 g	ESCOP 2003, Dorsch *et al.* 2002
10 – 16 years	0.5 – 1.0 g	Dorsch *et al.* 2002
	0.5 – 1.5 g	ESCOP 2003

Data from clinical trials

Combinations of herbal preparations of Primula root and thyme herb (Thymi herba) were the study medication in clinical trials with children. Data from such trials are assessed here only with respect to the actual posology of preparations of Primula root and with special emphasis on the reports of undesirable effects.

A combination Thymi herba + Primulae radix has been tested on 300 children (Fasse *et al.* 2006, Bässler & Zieseniß 2005).

100 g (77.5 ml) contain 1.8 g soft extract (1-2:1) (= herbal preparation F)

		amount soft extract		**corresponding amount herbal substance**
		single dose	**daily dose**	
under 1 year	2.5 ml 3 x daily	0.06 g	0.18 g	0.27 g root per day
1 – 3 years	3 ml 3 x daily	0.07 g	0.21 g	0.31 g root per day
3 – 6 years	5 ml 3 x daily	0.12 g	0.35 g	0.52 g root per day
6 – 12 years	5 ml 3-4 x daily	0.12 g	0.35 - 0.5 g	0.52 - 0.75 g root per day
12 – adult	5 ml 4 x daily	0.12 g	0.5 g	0.75 g root per day

The efficacy and tolerability of another combination of Thymi herba + Primulae radix (one product contained the herbal preparation D, another product the herbal preparation C) has been evaluated in a case series on 111 children in the age 1-4 years and 219 children between 4 and 12 years of age, in eight centres in Germany (Nauert & Grünwald 2005). The effective and well tolerated posology of Primulae radix is in accordance with the proposed posology for children:

100 g of one of these herbal medicinal products contained 20 g tincture of Primulae radix (1:5) (= herbal preparation D).

All children received 150 drops per day, corresponding to approximately 0.2 g Primula root. Depending on the drop size the single dose corresponded to 0.3 - 0.5 ml tincture, the daily dose to 0.9 - 1.5 ml tincture.

100 g (75.36 ml) of the other herbal medicinal product contained 2.5 g of liquid extract of Primulae radix (1:2-2.5) (= herbal preparation C)

		amount liquid extract		**corresponding amount herbal substance**
		single dose	**daily dose**	
1 – 4 years:	15 ml daily	0.17 g	0.5 g	0.22 g root per day
4 – 12 years	30 ml daily	0.33 g	1.0 g	0.48 g root per day

The dosage used in the above-mentioned trials support the safe use of the liquid extract (herbal preparation C), the tincture (herbal preparation D) and the soft extract (herbal preparation F) in children in the tested dosage scheme. Since no safety data are available for the use of the comminuted herbal substance or other herbal preparations in children, the recommendations for a posology in children are restricted to the three mentioned herbal preparations.

The treatment of cough in children below 4 years of age needs supervision of a doctor, therefore the use in children is not recommended in that age category.

Proposed posology

Based on these data, the following posology is recommended for children between 4 and 12 years of age:

	Single dose	**Dosage frequency**	**Daily dose**
C) Liquid extract 4-12 years of age	0.33 g	3 times daily	1.0 g
D) Tincture 4-12 years of age	0.3 - 0.5 ml	3 times daily	0.9 - 1.5 ml
F) Soft extract 4-6 years of age	0.12 g	3 times daily	0.35 g
6-12 years of age	0.12 g	3 to 4 times daily	0.35 - 0.5 g

Dosage frequency: May be taken every 2 to 3 hours (up to 3 times daily)

When using liquid extracts and tinctures in children, the ethanol content should be taken into consideration; primarily non-ethanolic preparations should be used in children.

Duration of use

No restriction on the duration of use has been reported for Primula root. Medical clarification is advisable if after 8-10 days of treatment the symptoms do not improve (Dingermann & Loew 2003).

Nauert & Grünwald (2005) reported the use of a combination of Primula root and thyme herb in children from 1 – 12 years. The medication was given for 7 days with an excellent tolerability.

A similar mean duration of use has been chosen for the observational study in children (< 3-12 years) from Bässler & Zieseniß (2005), also with a combination of thyme and Primula root. The medication was effective and well tolerated.

Proposed wording for the monograph

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

3. Non-Clinical Data

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

The mode of the expectorant action of Primula saponins is not yet satisfactorily clarified. In literature there is a general agreement that saponins irritate locally the gastric mucosa, which provokes a reflex increase in bronchial secretion, and subsequently dilutes the mucus and reduces its viscosity (Hänsel *et al.* 1994, Boyd 1954, Hänsel & Sticher 2007, ESCOP 2003). Irritation of mucous membranes in the throat and respiratory tract by saponins may also cause an increase in bronchial secretion. In addition the surface-tension lowering action of saponins might help to reduce the viscosity of the sputum, facilitating its ejection (Hostettman & Marston 1995).

A very specific influence on the β_2-adrenergic receptors of alveolar cells has been reported for the saponins of *Hedera helix*, which is used for the same indications like Primula root (Häberlein & Prenner 2005). At present it is not known whether these effects are restricted to the saponins of Hedera.

***In vitro* experiments**

Effects on the respiratory tract

Nauert *et al.* (2005) studied the effect of liquid extracts of Primulae radix and Thymi herba alone and in combination on the LPS-induced release of interleukin-8 (IL-8). Primula inhibited dose-dependently the LPS-induced release of IL-8, while Thymus did only slightly influence this parameter. The inhibitory effect of the combination Primula/thyme was higher than the sum of the single extracts. The authors concluded that the mucolytic effect may be explained by this effect.

Antifungal, antibacterial and antiviral effects

Most of the published *in vitro* experiments deal with the antiviral, antimycotic and antibacterial activity, which are common properties of saponins independent of their plant source.

Wolters (1966) compared the antifungal and antibacterial effects of 30 herbal substances containing saponins. Among the preparations tested, Primula root extracts belonged to the group of extracts with the most pronounced fungistatic or fungicide effects, while the antibacterial effect was considerably lower. The author suggested that saponins may act as important resistance factors of the plants.

Tschesche & Wulff (1965) described both antifungal and antibacterial effects (e.g. against *Staphylococcus aureus*, *Escherichia coli*) of saponins from *Primula elatior*.

The total saponins isolated from *Primula acaulis* (= *Primula vulgaris* Huds.) were effective against various strains of *Candida albicans* at concentrations of 80 – 97 µg/ml (Margineanu *et al.* 1976). The antimycotic effect of these saponins is quantitatively less than that of the typical antimycotics nystatine and stamicine. The aglycones of the saponins of *Primula vulgaris* root are identical to those found in the roots of *Primula elatior*.

An unspecified saponin mixture from *Primula veris* exhibited activity against influenza (A2/Japan 305) virus, producing 89% inhibition at a concentration of 6.2 µg/ml (Rao *et al.* 1974, Büechi 1996).

Other effects

A hexane extract (50 µg/ml) of *Primula veris* root inhibited COX (cyclooxygenase)-1 and COX-2 by 54% and 66% respectively (Lohmann *et al.* 2000).

Oswiecimska *et al.* (1975) described antimitotic activity of saponin fractions and extracts from Primulae radix and other herbal substances when using the Allium test.

***In vivo* experiments**

Effects on the respiratory tract

An undefined mixture of saponins from Primula root, at a concentration of 1:10,000, increased the ciliary activity of throat epithelium in curarised frog. This effect was explained by a reduced mucus surface tension. The ciliary activity was less at a concentration of 1:6,000 and ceased at 1:3,000 due to toxic effects (Vogel 1963).

In vivo studies (rabbit) on pharmacological/toxicological effects of extracts from Primula flower showed a significant increase in the production of bronchial secretion at the concentrations tested (Chibanguza *et al.* 1984). The observed effect was in the same range as secretory effects obtained with the reference substances bromhexin and acetylcysteine, which were also tested. Even though these studies were carried out with extracts from Primula flower, they are of some interest, because both roots and flowers contain saponins. The German Commission E actually gave the same indications to both Primula flower and Primula root.

Further *in vivo* experiments

An unspecified saponin of Primula root, administered parenterally, inhibited the growth of Walker carcinoma in rats with an ED_{50} of 40 mg/kg (Tschesche & Wulff 1973). However, considering the LD_{50} of 70 mg/kg this dose was too toxic and therefore less significant for practical application.

Sufka *et al.* (2001) tested herbal extracts for their anxiolytic properties in the chick social separation-stress procedure. For *Primula veris* (plant part not mentioned) no sedative effects were observed and no alteration of stress responses could be detected.

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

No data available.

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

Oral toxicity

There are no Primula-specific toxicity data available.

In the United States, root and flower of *Primula veris* and *Primula elatior* are classified as Class 1 botanicals, which means they can be safely consumed when used appropriately (McGuffin *et al.* 1997).

Data on saponins in general

After oral administration of saponins, no signs of absorption of toxic doses were found during *in vivo* studies in rats. Damages in liver metabolism and fatty degeneration of kidney cells were observed with higher oral doses of saponins (Vogel 1963).

The oral toxicity of saponins in mammals is relatively low, due to their poor absorption. LD_{50} values are in the range of 50 mg/kg (which is not very low when the figures are correct) and 1,000 mg/kg, (Hostettman & Marston 1995, Oakenfull 1981).

The dietary intake of saponins has been estimated as 10 mg per person per day in an average UK family. For vegetarians this figure is substantially higher, sometimes exceeding 200 mg per person per day. With a few exceptions (such as liquorice), no negative effects are apparent from prolonged intake of edible plants containing saponins. Primula saponins are considered to have a favourable benefit-risk ratio (Hostettman & Marston 1995).

Some toxicological information may be taken from *in vivo* studies with a primula flower extract on rabbits, which was performed by Chibanguza *et al*. (1984). Except for the red blood cell count, none of the parameters tested (respiration rate, pulse rate, prothrombin time, electrolyte concentrations of calcium, potassium and sodium) was influenced by the intragastral application of the extract from Primulae flower in the 50-fold therapeutic concentration.

Parenteral toxicity, toxicity of topical application

Hänsel *et al.* (1994) give toxicological data on Primula root: there are only LD values for the saponin fraction from *Primula veris* (LD_{50} mouse, i.p. 24.5 mg/kg b.w.) or for primula acid (LD_{50} rat, i.v. 1.2 mg/kg b.w.) available, which are not of relevance for the oral administration of Primula root preparations. The toxic effects of Primula root are primarily ascribed to the saponins which damage the cell membranes; this results in local irritation and, at higher doses, in cytotoxicity. After parenteral administration, haemolysis with liver and kidney lesions, cardiac dilatation and circulatory failure may occur. Local irritating effects have been observed on the rabbit cornea.

According to Vogel (1963) the parenteral toxicity is not correlated with the haemolytic index of the saponins *in vivo* (rats).

Other toxicity data

There are no data on genotoxicity, carcinogenicity, reproductive and developmental toxicity published.

3.4. Overall conclusions on non-clinical data

The non-clinical data on toxicology of Primula root preparations are incomplete, but available data indicate no signals of toxicological concern.

The contact allergic properties of different Primula species do not play a role after oral administration of underground parts and preparations thereof.

4. Clinical Data

4.1. Clinical Pharmacology

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

No data available.

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

No specific data are available on the pharmacokinetics of Primula root saponins. In general, saponins are poorly absorbed (Hostettman & Marston 1995). Usually glycosidic bonds are easily cleaved by enzymes of the gastrointestinal tract. The amount of absorption depends on the galenic form of the preparation (Hänsel & Sticher 2007).

4.2. Clinical Efficacy

Clinical studies relevant for the proposed indications

Clinical trials with Primulae radix as the only active ingredient

None published.

Clinical trials with combinations

Several clinical trials with combinations of Primula root and thyme are published (e.g. Gruenwald *et al*. 2005, Gruenwald *et al*. 2006, Kemmerich 2007). Since the efficacy of these combination products cannot be attributed to one of the active substances in the combination, these clinical trials cannot contribute to the clinical evidence of Primula root as the only active ingredient.

A critical assessment of these clinical trials is performed in the assessment report on the combination thyme and Primula root (EMA/HMPC/113577/2012).

Further clinical studies

In over 100 cases of antibiotic-resistant stomatitis caused by *Candida albicans*, the topical application of a solution of saponins from *Primula vulgaris* led to the disappearance of local symptoms within 2-3 days (Margineanu *et al.* 1976). According to the present publication all treated cases showed a rapid improvement of the subjective symptoms, and the local lesions disappeared within 2 – 3 days. Due to the lack of controls the results must be questioned, however a positive effect cannot be completely ruled out.

Saponins from Primula root are supposed to have anti-inflammatory properties and some protective effects on oedemas (Weyers 1992).

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

Clinical trials with Primulae radix as the only active ingredient

None published.

Clinical trials with combinations

The data from the clinical trials of combinations are used for the safety assessment in the paediatric population only.

***A controlled multi-centre study of herbal versus synthetic secretolytic drugs for acute bronchitis* (Ernst *et al.* 1997)**

Study: Controlled, multi-centre (771 general physicians), post-marketing surveillance study.

1,490 children 5.7 ± 2.9 years of age were included in the study group which received the fixed combination of thyme and Primula root. The other patients received Ambroxol (n=479 children), N-Acetylcysteine (n=299 children) or other herbal medicinal products (n=207 children, e.g. extracts of Hederae folium, thyme, combination of essential oils).

The study was neither randomised nor placebo-controlled.

These data are supportive to the safe use of the herbal preparation A in the monograph (dry extract (DER 3-9:1), extraction solvent ethanol 40-50% v/v).

The calculation of the odds ratios revealed that for any parameter (e.g. auscultation, coughing during day/night, pain while coughing, quantity of sputum, viscosity of sputum) the treatment was better with the fixed combination of thyme and Primula root compared to the other groups.

The rate of adverse events was clearly below 1% (in 1490 children 0.60%).

***Treatment of acute cold in children – results of an observational study with a Primula – thyme – preparation* (Fasse *et al.* 2006)**

These data are supportive to the safe use of the herbal preparation F in the monograph (soft extract (DER 1-4:1), extraction solvent ethanol 20-55% v/v)

100 g (77.5 ml) of the herbal medicinal product contained 1.8 g soft extract (1-2:1)

Posology:

		amount soft extract	
		single dose	**daily dose**
under 1 year	2.5 ml 3 times daily	0.06 g	0.18 g
1-3 years	3 ml 3 times daily	0.07 g	0.21 g
3-6 years	5 ml 3 times daily	0.12 g	0.35 g
6-12 years	5 ml 3 - 4 times daily	0.12 g	0.35 - 0.5 g
12 years-adult	5 ml 4 times daily	0.12 g	0.5 g

Side effects: no data; the authors state an 'excellent tolerability'. In 4 children vomiting occurred (2 children <3 years, 1 in group 3-6 years, 1 in group 6-12 years).

Assessor's comment: No control group, therefore no judgement of the efficacy of the treatment possible.

***Treatment of acute cold in children – results of an observational study with a Primula – thyme – preparation* (Bässler & Zieseniß 2005)**

Assessor's comment: No control group, therefore no judgement of the efficacy of the treatment possible. This study is published as congress abstract only. This paper seems to be the abstract of the paper by Fasse *et al.* (2006, see above).

***Efficacy and tolerability of liquid dosage forms of a fixed combination of thyme and primrose in children with acute bronchitis* (Nauert & Grünwald 2005, Grünwald *et al.* 2006a)**

The efficacy and tolerability of 2 other combinations of Thymi herba + Primulae radix have been evaluated in a case series on 111 children in the age 1 to 4 years and 219 children between 4 and 12 years in eight centres in Germany.

These data are supportive to the safe use of the herbal preparations C and D in the monograph.

The effective and well tolerated posology of Primulae radix is in accordance with the proposed posology for children:

100 g of the herbal medicinal product contained 20 g tincture of Primulae radix (1:5) (= herbal preparation D)

All children obtained 150 drops per day, corresponding to app. 0.2 g Primula root. Depending on the drop size the single dose corresponded to 0.3 - 0.5 ml tincture, the daily dose to 0.9 - 1.5 ml tincture.

100 g (75.36 ml) of a similar herbal medicinal product contained 2.5 g of liquid extract of Primulae radix (1:2-2.5) (= herbal preparation C)

		amount liquid extract	
		single dose	**daily dose**
1-4 years:	15 ml daily	0.17 g	0.5 g
4-12 years	30 ml daily	0.33 g	1.0 g

***Fixed combination of thyme liquid extract and Primula root liquid extract for the oral treatment of children with cough and bronchial catarrh* (Nauert & Eckert 2003, Grünwald *et al.* 2006a)**

Study: Non-interventional study in 312 children (1-4 years of age) and 324 children (4-12 years of age).

These data are supportive to the safe use of the herbal preparation C in the monograph.

Posology:

1-4 years: 2.5 ml 6 times daily

4-12 years: 5 ml 6 times daily

The onset of the treatment effect was observed at day 3-4.

The authors state an 'excellent tolerability' of the herbal preparation.

Assessor's comment: This study is published as congress abstract only. No control group was included, therefore no judgement of the efficacy of the treatment is possible. However, the study can be used for the demonstration of safety of the herbal preparation in children from 1 year up.

***A fixed combination of thyme and primrose for the treatment of cough* (Schmidt 2008)**

Study: Non-interventional study in 199 children 6-12 months of age.

These data are supportive to the safe use of the herbal preparation C in the monograph.

Posology: 6 times 1 ml per day

Mean duration of treatment: 6.4 days

Inclusion criterion: acute disorders of the upper respiratory tract with cough, catarrh and mucous obstruction of the bronchia.

Rating of symptoms like 'severity of cough', 'number of coughing fits per day', 'number of coughing fits during night', 'impairment of sleep quality'.

Side effects: 1 adverse event with possible causal relationship to the study medication (perioral eczema). 1 adverse event (vomiting, diarrhoea) was interpreted as correlated with the underlying disease.

Ethanol: 1 ml of the study medication results in a blood ethanol concentration of 0.008 ‰ . The metabolism in children in this age group is about 0.06 ‰ -0.09 ‰ per hour. Therefore no accumulation is to be expected.

Assessor's comment: No control group was included, therefore no judgement of the efficacy of the treatment is possible. Although the ethanol content is very low, the herbal preparation is not recommended for children below 2 years of age (according to the 'Reflection paper on ethanol content in herbal medicinal products and traditional herbal medicinal products in children', EMA/HMPC/85114/2008, published in January 2010).

***Compliance, tolerability and efficacy of a fixed combination of thyme and Primula (T+P) in 200 infants with acute bronchitis* (Nauert & Bentley 2008)**

Study: 200 infants (6-12 months of age) treated in 6 centres in Germany.

These data are supportive to the safe use of the herbal preparation C in the monograph.

Posology: The study medication was given in a dosage of 1 ml, 6 times daily.

Duration of use: The study medication was given over a period of 7 days.

The authors state an 'excellent tolerability' of the herbal preparation.

Assessor's comment: This study is published as congress abstract only. No control group was included. Therefore no judgement of the efficacy of the treatment is possible. This paper seems to be the abstract of the paper by Schmidt (2008, see above).

Assessor's general comments on the studies with the fixed combination containing the herbal preparations C and D that included children: Parts of the studies are published as abstracts. Grünwald *et al.* 2006a combined the data obtained until 2006. The numbers of included children differ between the publications.

Assessor's comment: The dosage used in the above mentioned trials support the safe use of the liquid extract (herbal preparation C), the tincture (herbal preparation D) and the soft extract (herbal preparation F) in children in the tested dosage scheme. Since no safety data are available for the use of the comminuted herbal substance or other herbal preparations in children, the recommendations for a posology in children between 4 to 12 years of age are restricted to the three mentioned herbal preparations.

Although there are available data on the safe use of some fixed combinations even in children below 1 year of age, the age limit should be set at 4 years of age for those herbal preparations where data on the safe use in the paediatric population are available. For safety reasons, the use of expectorants in children below 4 years of age has to be restricted, the treatment has to be performed under medical control. Moreover, recent guidelines for the management of cough in children recommend a 'wait, watch, review' approach instead of an intervention by medication (Kelley & Allen 2007).

All other herbal preparations of Primula root should be limited for adolescents above 12 years of age, adults and elderly.

4.3. Overall conclusions on clinical pharmacology and efficacy

Controlled clinical studies with preparations containing Primula root as the only active ingredient are lacking. Therefore only traditional use is possible for such herbal preparations. The clinical evidence of the combination of Primula root and thyme herb are assessed separately.

5. Clinical Safety/Pharmacovigilance

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

No data from clinical trials with medicinal products containing herbal preparations of Primula root as the only active ingredient are available. From clinical trials with combination products only information regarding adverse events is given.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

Adverse events

Many references (e.g. ESCOP 2003, Hänsel *et al.* 1994, Commission E (cited in Blumenthal *et al*. 1998), Dingermann & Loew 2003, Hänsel & Sticher 2007) mention the possible occurrence of gastric disorders and nausea in single cases. Vomiting and diarrhoea may also occur, but were described almost exclusively in case of overdose.

Bässler & Zieseniß (2005) published an observational study with a thyme/Primula combination in 300 children up to 12 years (< 3 years: 98 children; 3-6 years: 112 children; 6-12 years: 90 children) which was performed by 15 paediatric practitioners. Only in 4 children a non-serious undesirable effect occurred (vomiting).

Nauert & Grünwald (2005) tested in a case series the tolerability of a combination Thymus/Primula in 111 children from 1 to 4 years of age and 219 children between 4 and 12 years of age. The tolerability was rated as excellent.

The search in the database of the Austrian Medicines and Medical Devices Agency (accessed 2012-01-04) had only 3 reports of adverse effects referring to preparations containing Primula. All reports concern a combination product containing a liquid extract of Primulae flos and four other herbal preparations. Two minor allergic effects are reported (rash, facial oedema), the third report refers to an anaphylactic shock after concomitant use of this herbal medicinal product with Novalgin®, Parkemed® and Tricef®, which thus cannot be causally assigned to the presence of Primula. These reports are not relevant for preparations containing Primulae radix.

In the WHO database (access February 2012) only case reports are listed concerning combination products with Primulae radix and other herbal preparations. A causal relationship between the reported symptoms (mainly allergic symptoms, vomiting, abdominal pain) and Primulae radix cannot be established.

Contact allergic properties have been described for primin and other quinoid compounds obtained from *Primula elatior* and *Primula veris* (Hausen 1978). However, primin and other quinoid compounds occur in the aerial parts only (Hausen 1978). The clinical relevance of these contact allergic properties is therefore unlikely for the oral administration of Primula root preparations.

Serious adverse events and deaths

No serious events or deaths are reported.

Proposed wording for the monograph, section 'Special warnings'

Caution is recommended in patients with gastritis or gastric ulcer.

Proposed wording for the monograph, section 'Undesirable effects'

None reported.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Interactions

No interactions have been reported.

Saponins in general are considered to enhance the absorption of other substances in the gastrointestinal tract (Hänsel & Sticher 2007). It is assumed that saponins reduce the particle size of substances which are poorly soluble in water. In addition the irritation of the mucous layer may ease the diffusion of other substances. It is postulated that these effects may be of relevance for flavones, phytosterols and silicic acid, but systematic investigations are lacking. No specific data are available for the saponins of Primula species. Walthelm *et al.* (2001) studied the effect of saponins on the water solubility of model compounds. The Primula saponins showed no clear dose-dependent effect. The authors concluded that saponins in general should not be regarded as solubilisers.

Use in pregnancy and lactation, influence on fertility

Safety during pregnancy and lactation has not been established. No adverse effects have been reported from the use of Primula root as a medicinal product during pregnancy and lactation.

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

Overdose

Very high doses may lead to nausea, stomach upset, vomiting or diarrhoea (Wichtl & Neubeck 2006, Hänsel *et al.* 1994, Dingermann & Loew 2003, Wichtl 2004).

Contraindications

In the ESCOP monograph (2003) "gastritis and gastric ulcer" are mentioned as contraindications. In contrast to the ESCOP proposal, "gastritis" and "gastric ulcer" are not mentioned as absolute contraindications in any of the otherwise published literature. Therefore the assessors are of the opinion that gastritis and gastric ulcer should not be mentioned in the contraindication section (section 4.3.) of the SPC of a medicinal product, but instead, a warning in section 4.4. of the SPC is more appropriate.

Proposed wording for the monograph, section 'Contraindications'

Hypersensitivity to the active substance.

5.6. Overall conclusions on clinical safety

No serious adverse events or deaths were either reported from the medicinal use of the herbal preparations or observed during clinical trials with combinations of Primula and thyme.

In clinical trials with combinations of Primula and thyme only mild to moderate, transient gastrointestinal complaints or skin reactions occurred.

Although the data from clinical trials with combinations of Primula and thyme suggest that the use of some of the fixed combinations might be safe in children down to 6 months of age, the use of these herbal preparations of Primula root as an expectorant without supervision of a doctor should be restricted to children older than 4 years of age. All those herbal preparations where no data on the safe use in the paediatric population are available should be restricted to adolescents and adults.

The use of herbal preparations of Primula root can be considered as safe when administered at the specified posology.

6. Overall conclusions

The expectorant effects of Primula root preparations have long been recognised empirically; the medicinal uses are made plausible by the long-standing use and experience as well as pharmacological data (level of evidence 4). Controlled clinical studies are lacking. Although antibacterial and antimycotic effects have been described for Primula root saponins, these effects have never been verified in controlled clinical studies, and they are without importance for the traditional use of Primula root preparations in upper respiratory tract symptoms.

In conclusion, Primula root preparations can be regarded as traditional herbal medicinal products.

Since data on genotoxicity are lacking, no Community list entry can be proposed.

Annex

List of references