European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON
PRIMULA VERIS L., *PRIMULA ELATIOR* (L.) HILL, RADIX

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I. REGULATORY STATUS OVERVIEW[1]

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	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combinations
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:	
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 product on the market
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Standard marketing authorization
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:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combinations
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:	Only in combinations
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:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only in combinations

[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

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

***Primula veris* L., *Primula elatior* (L.) Hill, radix**

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)	*Primula veris* L., *Primula elatior* (L.) Hill, radix
Herbal preparation(s)	A) Dry extract (3-9:1), extraction solvent ethanol 40-50 % (v/v) B) Liquid extract (1:1), extraction solvent ethanol 70 % (v/v), C) Liquid extract (1:2.0-2.5), extraction solvent ethanol 70% (v/v) D) Tincture (1:5), extraction solvent ethanol 70 % (v/v) E) Soft extract (5-10:1), extraction solvent water F) Soft extract (1-4:1), extraction solvent ethanol 20-55% (v/v) G) Soft extract (6-10:1), extraction solvent methanol, water, ammonia solution 10% (50.0:49.5:0.5) H) Soft extract (6-10:1), extraction solvent methanol 50% I) Comminuted herbal substance for tea preparation
Pharmaceutical forms	Herbal substance or comminuted herbal substance for tea preparation or other herbal preparations in liquid and solid dosage forms for oral use.
Rapporteur	Heribert Pittner

II.1 INTRODUCTION

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

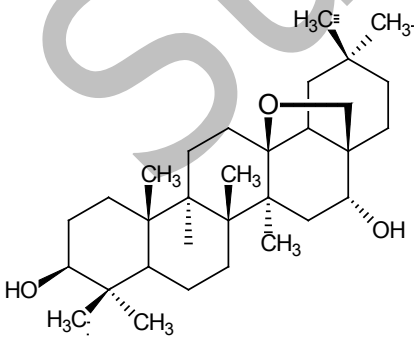
Herbal substance(s)

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.

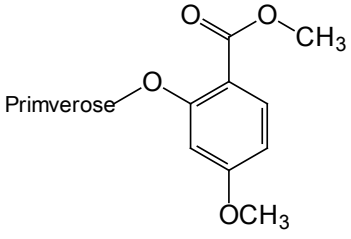
Constituents (Hänsel *et al.* 1994, Wichtl 2004, Hänsel & Sticher 2007, Tschesche & Ballhorn 1975, Tschesche *et al.* 1983):
The characteristic constituents are triterpene saponins (usually 3 – 10 [-12]%) and phenolic glycosides.
The triterpene saponins are of the oleanane type with branched sugar chains 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 *P. veris* are anagalligenin, priverogenin B and priverogenin B-22-acetate, important saponins are primacrosaponin (which has been isolated from *P. 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 drug 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.

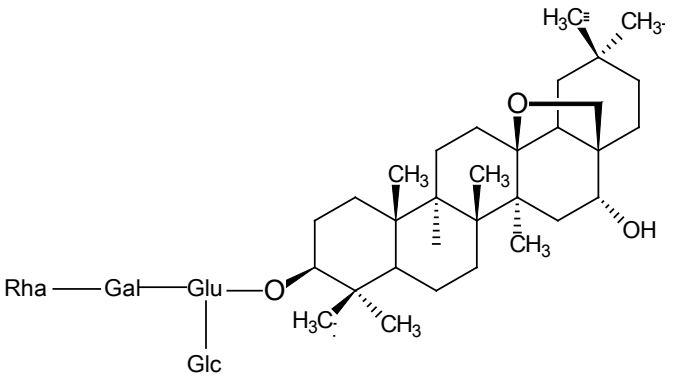
The phenolic glycosides primverin and primulaverin occur in both species in very variable amounts up to 2.3%, they are 2-primeverosides of 4-methoxy- and 5-methoxysalicilyc acid methyl esters (Thieme & Winkler 1971). These substances change during drying into the odoriferous aglycones (Wichtl 2004).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



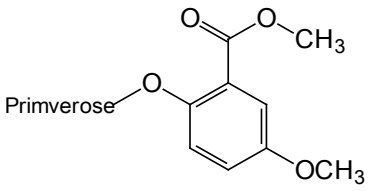
Protoprimulagenin A



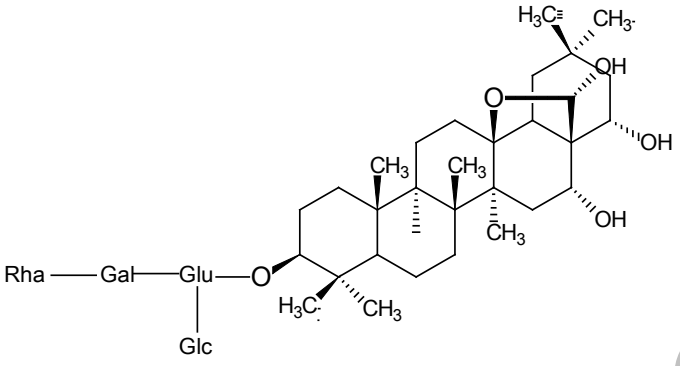
Primulaverin



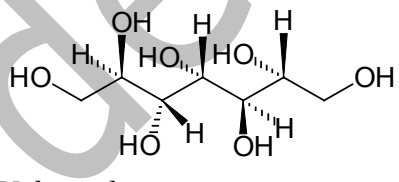
Primulasaponin



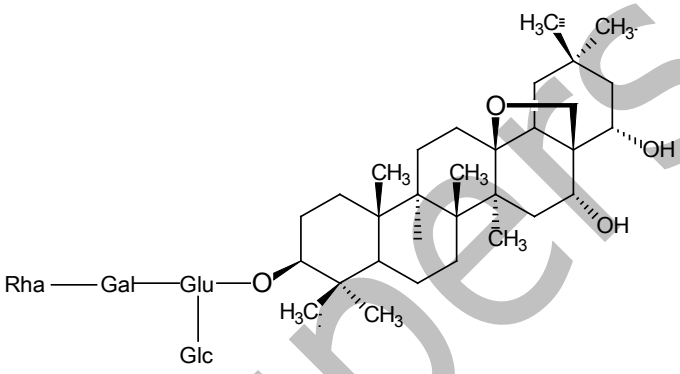
Primverin



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) since decades 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 app. 25%

B) Liquid extract (1:1), extraction solvent ethanol 70% (m/m): HI 2.700 – 3.300, corresponding to a saponin content of app. 7.5%

C) Liquid extract (1:2.0-2.5), extraction solvent ethanol 70% (v/v)

D) Tincture (1:5), extraction solvent ethanol 70 % (v/v); the tincture in the ÖAB 2008 is specified with a HI of 490 – 600, corresponding to a saponin content of app. 1.36%

E) Soft extract (5-10:1), extraction solvent water

F) Soft extract (1-4:1), extraction solvent ethanol 20-55% (v/v)

G)) Soft extract (6-10:1), extraction solvent methanol, water, ammonia solution 10% (50.0:49.5:0.5)

H) Soft extract (6-10:1), extraction solvent methanol 50%

I) Comminuted herbal substance

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

Combinations of herbal substance(s) and/or herbal preparation(s)

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.

Vitamin(s)

Not applicable.

Mineral(s)

Not applicable.

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

The underground organs of *P. veris* and *P. 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 those days the herbal substance as well as several herbal preparations have been in medicinal use. For the above mentioned herbal preparations the evidence for at least 30 years of medicinal use including 15 years in the Community could be verified. Therefore, for primula root and the mentioned preparations the qualification as a traditional herbal medicinal product is easily fulfilled.

II.1.2.1 Type of tradition, where relevant

European tradition.

II.1.2.2 Bibliographic/expert evidence on the medicinal use

II.1.2.2.1 Evidence regarding the indication/traditional use

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 1990, ESCOP monograph 2003, Wichtl 2004
(Chronic) bronchitis	Wichtl & Neubeck 2005; 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."

II.1.2.2.2 Evidence regarding the specified strength

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.

II.1.2.2.3 Evidence regarding the specified posology

Posology in adults:

Herbal substance and 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. Francaise, Xe	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 x daily*	*7.5 g*

1 Teaspoon = approximately 3.5 g.

Herbal Preparations:

A) Dry extract		
ÖAB 2008	single dose 0.1-0.2 g	0.3-0.6 g
Pharm. Francaise Xe		0.2-0.5 g
B) Liquid extract		
ÖAB 2008	single dose 0.5 g	1.5 g

C) Liquid extract		
Hänsel 1994	single dose 0.5 g	1.5 g
Weiß 1991	20 drops (0.6 g) 4 x daily	2.4 g
D) Tincture		**daily dose**
DAB 10 commentary		1.5-3 g
ÖAB 2008	single dose 0.5-1 g	1.5-3 g
DAB 9 commentary	single dose 0.3-1 ml	1-3 ml
Hänsel 1994	single dose 0.5-1 g	1.5-3 g
Ergänzungsband 6	single dose 2.5 g	7.5 g
Commission E		1.5-3 g
Auster & Schäfer 1961	mean single dose 2.5 g	7.5 g
Weiß 1991	20 drops 4 x daily	2.5 g
G) Soft extract		
Information from the German authorities	22.5 mg	67.5 mg

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

	single dose	**daily dose**
Herbal substance, 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 asked from 500 paediatricians by 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 several 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 (Phytobronchin-liquid) has been tested on 300 children (Bässler & Ziesenіß 2005, see also II.3.3.2 'Adverse events'). The posology for children in the SPC is congruent with the proposed data in literature (Dorsch *et al.* 2002):
100 g (77.5 ml) Phytobronchin-liquid contain 1.8 g soft extract (1-2:1, = herbal preparation type 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 (Bronchicum drops, Bronchicum Elixier S) were evaluated in a case series in 111 children of the age 1-4 years and 219 children between 4 and 12 years of age in eight centres in Germany (Nauert & Grünwald 2005, see also II.3.3.2 'Adverse events'). The administered dose was well tolerated:
100 g Bronchicum drops contain 20 g tincture of Primulae radix (1:5) (= herbal preparation type D)
All children obtained 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 0.9-1.5 ml tincture.

100g (75.36 ml) Bronchicum Elixier S contain 2.5 g of liquid extract of Primulae radix (1:2-2.5) (= herbal preparation type C)

		amount soft 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 supports the safe use of the liquid extract type C, the tincture (herbal preparation type D) and the soft extract type F in children in the tested dosage scheme. Since no safety data are available for the use of the herbal substance or other herbal preparations in children the recommendations for posology in children are restricted to the mentioned herbal preparations.
The treatment of cough in children below 4 years of age needs the supervision of a doctor, therefore, the use in children is not recommended in that age category.

The proposed posology for children is:

	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 tinctures in children, the ethanol content should be taken into consideration. Primarily non-ethanolic preparations should be used in children.

II.1.2.2.4 Evidence regarding the route of administration

The oral administration is the only route of administration for primula root preparations in the recommended traditional indication.

II.1.2.2.5 Evidence regarding the 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 seven 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:

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

II.1.3 Assessor's overall conclusion on the traditional medicinal use

Preparations from primula root have been used for the relief of symptoms of the upper respiratory tract in coughs and colds for many decades. Since the clinical documentation is poor and no controlled clinical studies are available, the use of primula root preparations has to be regarded as traditional.

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available 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).

Recently 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 conclude 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) has compared the antifungal and antibacterial effects of 30 herbal drugs containing saponins. Among them, 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* (= *P. 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 *P. vulgaris* root are identical to those found in the roots of *P. elatior*.

An unspecified saponin mixture from *Primula veris* exhibited activity against influenza (A_2/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 ED50 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.

II.2.1.2 Assessor's overall conclusions on pharmacology

The results of the pharmacological tests make the use of herbal preparations of primula root as an expectorant plausible.

II.2.2 Pharmacokinetics

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).

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

No data available.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

No specific data are available on the pharmacokinetics of primula root saponins.

II.2.3 Toxicology

II.2.3.1 Overview of available 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 *P. veris* and *P. elatior* are classified as Class 1, 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. Damages in liver metabolism and fatty degeneration of kidney cells were observed during *in vivo* studies in rats with higher oral doses of saponins (Vogel 1963).

The oral toxicity of saponins in mammals is relatively low, due to their poor absorption. LD50 values are in the range of 50 mg/kg (which is not very low when the figures are correct) and 1000 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 count, none of the parameters tested (respiration rate, pulse rate, prothrombin time, electrolyte concentrations of calcium, potassium, sodium) was influenced by the intragastral application of the extract from primula 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 *P. veris* (LD_{50} mouse, *i.p.* 24.5 mg kg^{-1} b.w.) or for primula acid (LD_{50} rat, *i.v.* 1.2 mg kg^{-1} 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, in 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.

II.2.3.2 Assessor's overall conclusions on toxicology

The oral administration of primula root preparations can be regarded as safe, especially at therapeutic doses; the contact allergic properties of different primula species do not play a role after oral administration of underground parts and preparations thereof.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

No data available.

II.3.1.1 Pharmacodynamics

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

Not applicable.

II.3.1.2 Pharmacokinetics

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 specific data are available on the pharmacokinetics of primula root saponins. In general, saponins are poorly absorbed by the body (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).

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

No specific data are available on the pharmacokinetics of primula root saponins.

II.3.2 Clinical Efficacy[3]

II.3.2.1 Dose response studies

No data available.

II.3.2.2 Clinical studies (case studies and clinical trials)

Clinical studies relevant for the proposed indications

Clinical trials with Primulae radix as the only active ingredient:

None published.

Clinical trials with combinations:

Study on Bronchipret film coated tablets (60 mg dried extract of Primulae radix DER 6-7:1, solvent ethanol 47.4% v/v; 160 mg dried extract of Thymi herba DER 5.9-10:1, solvent ethanol 70% v/v) (Ernst *et al.* 1997):
In this controlled multi-centre study the medication was compared with other pharmacotherapeutic options for acute bronchitis (e.g. ivy extract, ambroxol). 7783 patients were included. The study was neither randomised, nor placebo-controlled. The findings imply that a benefit-risk evaluation would favour the thyme-primula combination over synthetic drugs for acute bronchitis.

Grünwald *et al.* (2005) tested the efficacy and tolerability of a combination of Thymi herba and Primulae radix (Bronchicum drops) in a randomized, double-blind, prospective, placebo-controlled, multi-centre clinical trial. 150 adult outpatients suffering from acute, not previously treated bronchitis, lasting for less than 48 hours were included. The dosage was 1 ml five times daily (corresponding to 0.2 g primula root). The authors conclude that the study demonstrated efficacy in acute bronchitis. The therapeutic effect was more pronounced the stronger the severity of acute bronchitis was. The medication was well tolerated.

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

In a single-blind, randomised, bi-centric clinical trial Grünwald *et al.* (2006) compared different preparations of a combination of Thymi herba and Primulae radix (Bronchicum drops, Bronchicum Elixier S). 189 outpatients suffering from acute bronchitis were included. Both medications showed similar efficacy and were well tolerated.

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).

II.3.2.3 Clinical studies in special populations (e.g. elderly and children)

Bässler & Zieseniß (2005) describe an observational study with a thyme/primula preparation (Phytobronchin Saft) in 300 children up to 12 years (< 3 years: 98 children; 3 – 6 years: 112 children; 6 – 12 years: 90 children) by 15 paediatric practitioners. An improvement of different cough symptoms and derived symptoms caused by cough (e.g. sleep disturbances) was reported in all patient groups. Only in 4 children a non-serious undesirable effect occurred (vomiting). The value of this study is limited due to the open design, nevertheless, it demonstrates the use of a primula preparation in children below 3 years of age.

Nauert & Grünwald (2005) tested in a case series the tolerability of a combination thyme/primula (Bronchicum drops, Bronchicum Elixier S) in 111 children from 1-4 years and 219 children in the age between 4 and 12 years. After 3-4 days of treatment a considerable improvement of the symptoms could be observed in 81% of the patients, in 64% the symptoms disappeared after 6 days. The tolerability was rated as excellent and no undesirable effects were observed. The value of this study is also limited due its open design.

II.3.2.4 Assessor's overall conclusions on clinical 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 should be assessed separately.

II.3.3 Clinical Safety/Pharmacovigilance

II.3.3.1 Patient exposure

No exact data on patient exposure are available.

II.3.3.2 Adverse events

Many references (e.g. ESCOP 2003, Hänsel *et al.* 1994, Commission E, 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 (Phytobronchin Saft) 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 thyme/primula (Bronchicum drops, Bronchicum Elixier S) in 111 children from 1-4 years and 219 children in the age 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 AGES PharmMed (accessed 2006-12-12) had only 3 reports of adverse effects referring to preparations containing primula. All reports concern the product Sinupret, which is a combination of a liquid extract of Primulae flos and four other herbal preparations. 2 minor allergic effects are reported (rash, facial oedema), the third report refers to an anaphylactic shock after concomitant use of Sinupret, Novalgin, Parkemed and Tricef, which cannot be causally assigned to the presence of primula. These reports are not relevant for preparations containing Primulae radix.

In the WHO database (accessed December 2006) one report is listed, which refers to a combination of Primulae radix, Thymi herba and Droserae herba. The use of this preparation is associated with the occurrence of dermatitis, skin discolouration and bullous eruption in a four-year old child.

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.

Wording for the monograph, section 'Undesirable effects':

"Gastric disorders, nausea, vomiting and allergic reactions may occur. The frequency is not known.

If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted."

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), but instead, a warning in section 4.4 of the SPC is more appropriate.

Wording for the monograph, section 'Contraindications':

"Hypersensitivity to the active substance or to other primula species.
Children with a history of acute obstructive laryngitis.
Asthma."

II.3.3.3 Serious adverse events and deaths

None known for primula root preparations for oral administration.

II.3.3.4 Laboratory findings

No data published.

II.3.3.5 Safety in special populations and situations

No data published.

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

None known.

II.3.3.5.2 Drug interactions

No interactions have been reported.
Saponins in general are considered to enhance the absorption of other substances in the gastro-intestinal 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 conclude that saponins in general should not be regarded as solubilisers.

II.3.3.5.3 Use in pregnancy and lactation

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.

II.3.3.5.4 Overdose

Very high doses may cause nausea, stomach upset, vomiting or diarrhoea (Wichtl & Neubeck 2005; Hänsel *et al*. 1994, Dingermann & Loew 2003, Wichtl 2004).

II.3.3.5.5 Drug abuse

None known.

II.3.3.5.6 Withdrawal and rebound

None known.

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

None known.

II.3.3.6 Assessor's overall conclusions on clinical safety

In the recommended dosage the use of herbal preparations of primula root can be considered as safe.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

The expectorant effects of primula root preparations have long been recognised empirically; the respective uses are made plausible by 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. Primula root preparations can therefore be regarded as traditional herbal medicinal products.

ABBREVIATIONS

DAB	Deutsches Arzneibuch, German Pharmacopoeia
Erg.-B. 6	Ergänzungsbuch zum Deutschen Arzneibuch,
HI	Haemolytical Index
ÖAB	Österreichisches Arzneibuch, Austrian Pharmacopoeia
Pharm. Eur.	European Pharmacopoeia
Pharm. Franc.	Pharmacopée Française, French Pharmacopoeia

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON *PRIMULA VERIS* L. AND *PRIMULA ELATIOR* (L.) HILL, RADIX

III.2 LITERATURE REFERENCES