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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

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

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ASSESSMENT REPORT

FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

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

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Primula veris* L., *Primula elatior* (L.) Hill, flos
Herbal preparation(s)	Liquid extract (1:1, extraction solvent ethanol 25%, v/v) Comminuted herbal substance
Pharmaceutical forms	Herbal substance or comminuted herbal substance for tea preparation or other herbal preparation in liquid and solid dosage forms for oral use.
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Assessors	Johann Krisper Reinhard Länger

1 INTRODUCTION

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

- **Herbal substance**

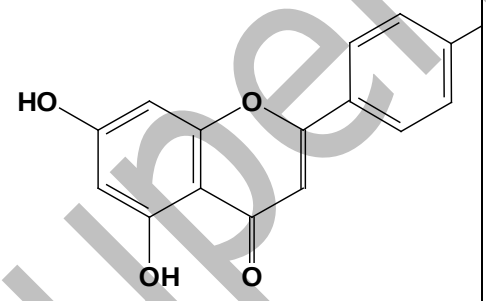
Primula flower (Primulae flos)

Whole or cut, dried flowers including the calyx or without calyx of *Primula veris* L. and/or *Primula elatior* (L.) Hill for oral administration. The material complies with the German Deutscher Arzneimittel Codex (DAC 2006).
Some references restrict the plant source to the species *Primula veris* (British Herbal Pharmacopoeia (1983), Pharmacopée Française X^{e} édition).

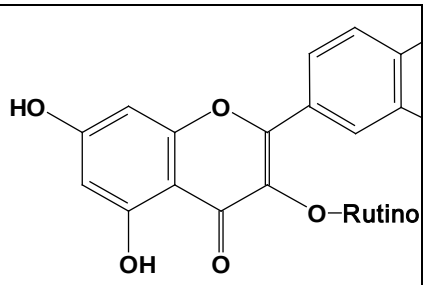
The haemolytic index (HI) has been used for biological standardisation of saponin containing herbal substances and herbal preparations. Although no longer in use the HI facilitates a comparison between the HI of a herbal drug and preparations thereof and allows an estimation of the saponin content.

HI of Primulae flos: 35

Constituents (Hänsel et al. 1994), Wichtl 2004):
Triterpene saponins (in the sepals up to 2%); structural details are missing.
Flavonoids (in the petals up to 3%): apigenine, rutoside (1.3% in *P. elatior*, 0.16 % in *P. veris*), quercetagenin-3-gentiobioside, 3',4',5' – trimethoxyflavone; kaempferol-3-rutinosid and isorhamnetin-3-glucoside present in flowers of *P. elatior* only.
Carotenoids, traces of essential oil, rosmarinic acid, D- volemitol and other sugar alcohols.

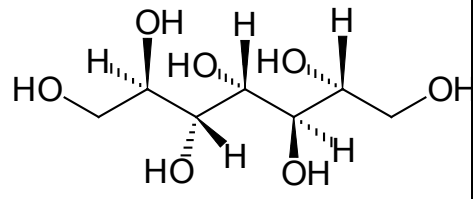


Apigenin

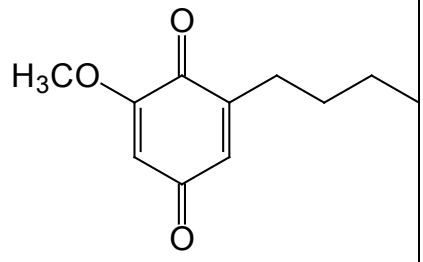


Rutoside

The aerial parts may contain primin and other quinoid compounds, which are responsible for contact allergenic properties of species of the genus Primula (Hausen 1978).



Volemitol



Primin

Herbal preparations with evidence of traditional use

Liquid extract (1:1, extraction solvent 25% ethanol (v/v), cited in the British Herbal Pharmacopoeia)

Assessors comment: no details could be found on the tincture which is cited in the publications of the Commission E.

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

Primula flower extracts are used in combinations with many other herbal substances/herbal preparations. This monograph refers exclusively to Primula flower.

Vitamin(s)

Not applicable

Mineral(s)

Not applicable

2 TRADITIONAL MEDICINAL USE

2.1 Information on period of medicinal use in the Community regarding the specified indication

Data concerning the medicinal use of Primula flower in Europe go back to the beginning of the 20th century (Zörnig 1911), Dinand 1921). The herbal substance and preparations are also mentioned in Hager's Handbuch (List & Hörhammer 1977). Therefore it can be stated that the crude drug is continuously in medical use since about 100 years.

Therefore, for Primula flower a period of at least 30 years in medical use as requested by Directive 2004/24/EC for the qualification as a traditional herbal medicinal product is easily fulfilled.

2.2 Type of tradition, where relevant

European tradition.

2.3 Bibliographic/expert evidence on the medicinal use

2.3.1 Evidence regarding the indication/traditional use

The following indications have been reported for Primula flower:

Ailments of the airways:

Cough	List & Hörhammer (1977),
Catarrhs of respiratory tract	Hänsel et al. (1994); Commission E (1990), Wichtl (2004), DAC (2006)
Expectorant for coughs and bronchitis	Wichtl (2004), Zörnig (1911)

Further indications:

Nervousness	List & Hörhammer (1977), Wichtl (2004), Fournier (1948), Zörnig (1911), Hänsel et al. (1994), British Herbal Pharmacopoeia (1983)
Headache	Wichtl (2004), Flamm et al. (1940), Zörnig (1911), Hänsel et al. (1994)
As a diaphoretic	Dinand (1921), List & Hörhammer (1977)
Rheumatism	List & Hörhammer (1977), Zörnig (1911)
Gout	List & Hörhammer (1977), Zörnig (1911)
As a diuretic	Zörnig (1911), Auster & Schäfer (1961)

Plausibility of actions: saponins are only present in the sepals; therefore for the indication 'cough' the complete flowers must be used.
Further constituents do not support other traditional indications.

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 specified indication exclusively based upon long-standing use."

2.3.2 Evidence regarding the specified strength

Primula flower is usually used in combination with other herbal substances. The content of Primula flower in herbal preparations varies in herbal teas from 10% to 30%, in liquid preparations it is about 1% and in solid dosage forms about 8%.

2.3.3 Evidence regarding the specified posology

<u>Posology in adults:</u>

Herbal substance

reference	single dose	daily dose
British Herbal Pharm. (1938)	1-2 g as infusion, 3 times daily	
Wichtl (2004)	1 teaspoon = 1.3 g	2-4 g
Ergänzungsbuch 6 (1941)	1 g	
DAC (2006)	1 teaspoon = 1.3 g	2.6-3.9 g
List & Hörhammer (1977)	single dose 1 g	
Hänsel et al. (1994)	single dose 1 g	3 g
Auster & Schäfer (1961)	1 g	
Commission E		2-4 g

1 Teaspoon = approximately 1.3 g

Herbal preparations

reference	single dose	daily dose
Tincture		
Commission E (1990)	0.8-2.5 g	2.5-7.5 g
Liquid extract		
British Herbal Pharm. (1983)	1-2 ml, 3 times daily	3-6 ml

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

	single dose	recommended mean daily dose
Comminuted herbal substance for tea preparation	1 g	2-4 g
Liquid extract	1-3 ml	3-6 ml

Dosage frequency: May be taken 3 times daily

Posology in children:
The posology presented in Dorsch et al. (2002) is calculated.

The authors propose for the herbal substance as mean daily dose:

	herbal substance, mean daily dose
0-1 year	0.5-1 g
>1-4 years	1-2 g
>4-10 years	2-3 g
>10-16 years	2-4 g

No data for a posology in children from clinical trials are available. Therefore Primula flower should not be used in children up to 12 years. Since data available for Primula root suggest a use for children from 1 year of age, a use of Primula flower from 12 years could be justified.
See 2.5.2 Special warnings.

2.3.4 Evidence regarding the route of administration

The oral administration is the only route of administration for Primula flower preparations in the recommended traditional indication.

2.3.5 Evidence regarding the duration of use

No restriction on the duration of use has been reported for Primula flower.

Adolescents over 12 years of age, adults, elderly
Medical attention should be sought if after 1 week of treatment the symptoms do not improve.

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

2.4 Assessor's overall conclusion on the traditional medicinal use

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

2.5 Bibliographic review of safety data of the traditional herbal medicinal substances/preparations

2.5.1 Patient exposure

No exact data on patient exposure are available.

2.5.2 Adverse events

All cited references (e.g. Hänsel et al. 1994, Commission E, Hänsel & Sticher 2007) agree that in single cases gastric disorders and nausea may occur.

Contact allergic properties have been described for primin and other quinoid compounds which may be present in the aerial parts of *Primula elatior* and *Primula veris* (Hausen 1978). For both species, primin-free as well as primin-containing individuals are reported (Hausen 1978, Fregert & Hjorth 1977). Hypersensitivity against primin could be of clinical relevance.

The search in the database of the Austrian Medicines and Medical Devices Agency AGES PharmMed (access date: 12 December 2006) 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 (Gentianae radix, Rumicis herba, Sambuci flos, Verbenae herba). The adverse effects cannot be exclusively assigned to Primula flower, the contribution of the combination partners is not known. In 2 cases, the application of Sinupret® caused allergic reactions (rash, face 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 flos as the only active ingredient.

In the WHO database (access December 2006), one report of allergic reaction after ingestion of Primula flower is listed, the type of preparation is not mentioned.

Wording for the monograph:

Special warnings:

The use is not recommended in children under 12 years of age because no data on safety are available.
Caution is recommended in patients with gastritis or gastric ulcer.
If dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted.
For extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

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.

2.5.3 Serious events and deaths

None known for Primula flower preparations for oral administration.

The anaphylactic shock observed after the concomitant application of Sinupret®, Novalgin®, Parkemed® and Tricef® cannot be causally assigned to Primulae flos present in Sinupret®.

2.5.4 Safety in special populations and situations

2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors

None known.

2.5.4.2 Drug-drug interactions and other interactions

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.

The dietary intake of saponins has been estimated as 10 mg per person per day in an average UK family. For vegetarians the figure is substantially higher, sometimes exceeding 200 mg per person per day (Hostettman & Marston 1995). Saponins administered with preparations of Primulae flower (4 g with 2% saponins in the sepals only) exceed slightly the one of typical dietary intake. It is not known whether this increase affects the absorption of other drugs.
No studies on interactions with other medications have been performed. No interactions have been reported.

2.5.4.3 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 flower as a medicinal product during pregnancy and lactation.

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

2.5.4.4 Overdose

Overdose may lead to stomach upset, vomiting or diarrhoea.

2.5.4.5 Drug abuse

None known.

2.5.4.6 Withdrawal and rebound

None known.

2.5.4.7 Effects on ability to drive and use machines

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

2.5.4.8 Contraindications (hypersensitivity and allergic potential to be both covered)

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

2.5.5 Non-clinical safety data

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

Oral toxicity

There are no Primula-specific toxicity data available.

In the United States, flowers of *Primula 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 have been 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. LD_{50} 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 the 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).

Chibanguza et al. (1984) have performed *in vivo* studies on rabbits which contain some information concerning toxicological considerations. Except for the red blood count, none of the parameters tested (rate of breathing, pulse rate, Quick-%-value, electrolyte concentrations of calcium, potassium, sodium) was influenced by the intragastral application of the extract from Primulae flos 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 have no relevance for the oral administration of Primula flower preparations. Saponins 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.

2.5.6 Assessor's overall conclusions on safe use

The oral administration of Primula flower preparations can be regarded as safe, especially at therapeutic doses; the contact allergic properties of different Primula species can cause rarely allergic reactions. The data available from pharmacovigilance databases do not show a serious risk for the use of Primula flower.

3 PHARMACOLOGICAL PROPERTIES

3.1 Overview of pharmacological effects of herbal substance(s), herbal preparation(s) and relevant constituents thereof on the basis of long-standing use and experience

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**

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).

Further *in vitro* experiments:

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 by means of the Allium test.

Herre (1937) published some data in rats concerning diuretic properties of *Primula officinalis* (= *Primula veris*), but there are no more recent investigations which endorse these findings.

***In vivo* experiments**

Experiments relevant for the proposed indications:

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 (Chibanzuga et al. 1984)). The observed effect was in the range as secretory effects obtained with the reference substances bromhexin and acetylcysteine which were also tested.

An undefined mixture of saponins from Primula root, at a concentration of 1:10,000, increased the ciliary activity of throat epithelium of 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).

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 LD50 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.

4 CLINICAL STUDIES

Clinical studies with preparations containing solely Primula flower do not exist.
The data generated in clinical trials with the special preparation Sinupret® cannot be included, because the contribution of the Primula flower extract to the overall-activity cannot be estimated.

5 PHARMACOKINETIC PROPERTIES

No specific data are available on the pharmacokinetics of Primula flower 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).

6 ASSESSOR'S OVERALL CONCLUSIONS

The expectorant effects of Primula flower preparations have long been recognised empirically; the respective uses are made plausible by pharmacological data (level of evidence 4). Controlled clinical studies are lacking.
In conclusion, Primula flower preparations can be regarded as traditional herbal medicinal products.