EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

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

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, flos
Herbal preparation(s)	A) Liquid extract (DER 1:1), extraction solvent ethanol 25% v/v B) 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.
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1. Introduction

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

- Herbal substance(s)

Primula flower (Primulae flos) consists of the whole or cut, dried flowers including the calyx or without calyx of *Primula veris* L. and /or *Primula elatior* (L.) Hill. 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 (1974), Pharmacopée Française Xème 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 an herbal substance and preparations thereof allows an estimation of the saponin content.

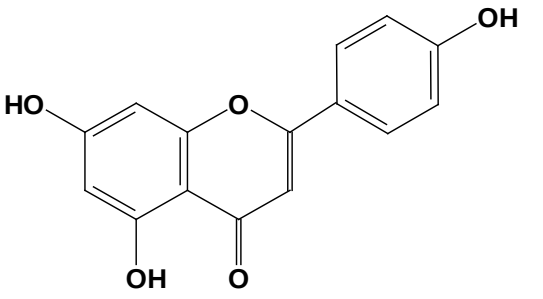
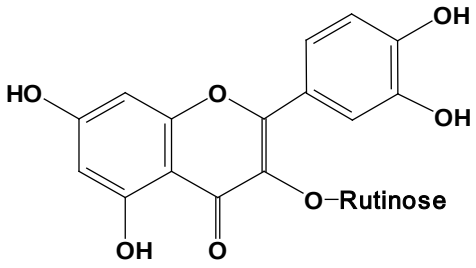
HI of Primulae flos: 35

Constituents (Hänsel *et al.* 1994, Wichtl 2004):

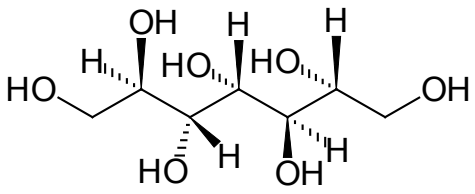
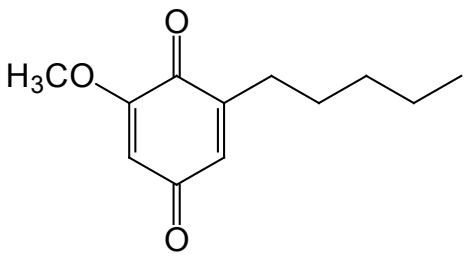
Triterpene saponins (in the sepals up to 2%); structural details are missing.

Flavonoids (in the petals up to 3%): apigenine, rutoside (1.3% in *Primula elatior*, 0.16% in *Primula veris*), quercetagenin-3-gentiobioside, 3',4',5' – trimethoxyflavone, kaempferol-3-rutinosid and isorhamnetin-3-glucoside present in flowers of *Primula 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 preparation(s)

Herbal preparations with evidence of traditional use:

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

Assessor's comment: no details regarding the DER or the extraction solvent could be found for the tincture which is cited in the publications of the Commission E (cited in Blumenthal *et al*. 1998) – see section 2.1.

- 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 flower extracts are used in combinations with many other herbal substances/herbal preparations.

This monograph refers exclusively to Primula flower.

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:	Combination products
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:	Combination products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combination products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combination products
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:	
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:	
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:	

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 January 2007; for the systematic review/revision of monograph: 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

Data concerning the medicinal use of Primula flowers 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). In the British Herbal Pharmacopoeia (1974) a liquid extract (1:1, extraction solvent 25% ethanol v/v) is mentioned.

Therefore it can be stated that the herbal substance and preparations thereof are continuously in medicinal use since about 100 years. Thus for Primula flower a period of at least 30 years of medicinal use including at least 15 years in the European Union (EU) as requested by Directive 2004/24/EC for the qualification as a traditional herbal medicinal product is fulfilled.

No details regarding the DER or the extraction solvent could be found for the tincture which is cited in the publications of the Commission E (cited in Blumenthal *et al*. 1998). Therefore this herbal preparation is not included in the monograph.

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

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 (cited in Blumenthal *et al*. 1998), 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 (1974)
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 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 flowers are usually used in combination with other herbal substances. The Primula content in these preparations varies in herbal teas from 10% to 30%, in liquid preparations it is about 1% and in solid dosage forms about 8%.

Posology in adults

Comminuted herbal substance

	single dose	**daily dose**
British Herbal Pharm. (1974)	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)	1 g	
Hänsel *et al.* (1994)	1 g	3 g
Auster & Schäfer (1961)	1 g	
Commission E (cited in Blumenthal *et al*. 1998)		2 - 4 g

1 teaspoon = approximately 1.3 g

Herbal preparations

	single dose	**daily dose**
Tincture		
Commission E (cited in Blumenthal *et al*. 1998)		2.5 - 7.5 g
Liquid extract		
British Herbal Pharm. (1974)	1 - 2 ml, 3 times daily	3 - 6 ml

Posology in adolescents

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
>10 - 16 years	2 - 4 g

Since data on Primula root suggest a use in children from 1 year of age and older, a use of Primula flowers in adolescents could be justified.

Proposed posology for adolescents over 12 years of age, adults and elderly

	single dose	**recommended mean daily dose**
Comminuted herbal substance as herbal tea	1 g	2 - 4 g
Tincture	0.8 - 2.5 g	2.5 - 7.5 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 - 12 years	2 - 4 g

No data for a posology in children from clinical trials are available. Therefore Primula flowers should not be used in children under 12 years of age.

Duration of use

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

Adolescents, 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.

3. Non-Clinical Data

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

No specific data for Primula flower are available.

The mode of the expectorant action of Primula saponins in general 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, which 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, and the surface-tension lowering action of saponins might help to reduce the viscosity of sputum, making it easier to eject (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 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 these drugs, Primula root extracts belong to the group of extracts with the most pronounced fungistatic or fungicide effects, while the antibacterial effect of Primula root extract is much less. The author regards saponins as possibly important resistance factors of the plants.

Tschesche & Wulff (1965) describe both antifungal and antibacterial effects (e.g. against *Staphylococcus aureus*, *Escherichia coli*) of Primula saponin (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 with those found in the roots of *Primula 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) have described antimitotic activity of saponin fractions and extracts from Primulae radix and other herbal substances by means of the Allium test.

Herre (1937) has given 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 of 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 curarized frog. This effect was assumed to be due to a decrease in surface tension of the mucus. 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 ED_{50} of 40 mg/kg, although this dose was too toxic in relation to the LD_{50} of 70 mg/kg to be of practical significance (Tschesche & Wulff 1973).

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, in addition 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, flowers 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 the figure is substantially higher, sometimes over 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) performed *in vivo* studies on rabbits which contain some information concerning toxicological considerations. 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 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 *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 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.

Vogel (1963) pointed out that, according to his *in vivo* studies with rats, parenteral toxicity is not correlated with the haemolytic index of the saponins.

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 flower preparations are incomplete, but available data indicate no signals of toxicological concern.

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 flower 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 flos as the only active ingredient

None published.

Clinical trials with combinations

The data generated in clinical trials with a fixed combination of herbal preparations of Primulae flos, Sambuci flos, Verbenae herba, Gentianae radix and Rumicis herba cannot be included, because the contribution of the Primula flower extract to the overall activity cannot be estimated.

Further clinical studies

Not applicable.

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 flos as the only active ingredient

None published.

Clinical trials with combinations

The data generated in clinical trials with a fixed combination of herbal preparations of Primulae flos, Sambuci flos, Verbenae herba, Gentianae radix and Rumicis herba cannot be included, because the contribution of the Primula flower extract to the overall-activity cannot be estimated.

4.3. Overall conclusions on clinical pharmacology and efficacy

Controlled clinical studies with preparations containing primula flower as the only active ingredient are lacking. Therefore only traditional use can be accepted for herbal preparations of Primulae flos.

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 flower as the only active ingredient are available.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

Adverse events

All cited references (e.g. Hänsel *et al.* 1994, Commission E [cited in Blumenthal *et al*. 1998], 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) had only 3 reports of adverse effects referring to preparations containing Primula (access date: 2012-01-04). All reports concern a combination product containing herbal preparations of Primulae flos, Gentianae radix, Rumicis herba, Sambuci flos and 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 this combination product caused allergic reactions (rash, face oedema); the

third report refers to an anaphylactic shock after concomitant use of this combination product with several other medicinal products. The adverse effect cannot be causally assigned to Primula flower. These reports are not relevant for preparations containing Primulae flos as the only active ingredient.

In the WHO database (access February 2012) one report of allergic reaction after ingestion of Primula flower and other medicinal products is listed (the type of preparation is not mentioned).

Allergic reactions may occur due to the possible presence of allergenic quinoid constituents.

The contact allergic properties of different Primula species may cause rarely allergic reactions.

Serious adverse events and deaths

The anaphylactic shock observed after the concomitant application of a combination product containing herbal preparations of Primulae flos, Gentianae radix, Rumicis herba, Sambuci flos and Verbenae herba and several other medicinal products cannot be causally assigned to Primulae flos.

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'

Allergic reactions may occur. The frequency is not known.

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 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 15 mg per person per day in an average UK family; for vegetarians the figure is substantially higher, sometimes over 200 mg per person per day (Hostettman & Marston 1995). Saponins administered with preparations of Primulae flowers (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.

Proposed wording for the monograph, section 'Interactions'

None reported.

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 flower 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).

Proposed wording for the monograph, section 'Overdose'

Overdose may lead to stomach upset, vomiting or diarrhoea.

Contraindications

No specific data available for Primulae flos. The constituents responsible for the contact allergic properties of different Primula species may be present in Primulae flos. Therefore hypersensitivity to other Primula species should be included in the section 'Contraindications'.

Proposed wording for the monograph, section 'Contraindications'

Hypersensitivity to the active substance or to other Primula species.

5.6. Overall conclusions on clinical safety

No serious adverse events or deaths were reported from the medicinal use of the herbal preparations in the monograph.

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

No data are available which could demonstrate the safe use of traditional herbal preparations of Primula flower in children. Based on the experience with Primula root, the use of herbal preparations of Primula flower in adolescents is acceptable.

6. Overall conclusions

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

In conclusion, Primula flower 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