EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/HMPC/560962/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix
Herbal preparation(s)	Liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m
Pharmaceutical forms	Herbal preparation in liquid dosage forms for oral use.

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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Table of contents

1. Introduction

Pelargonium species (*Geraniaceae*) indigenous to areas of southern Africa are highly valued by traditional healers for their curative properties. Among those traditional herbal medicines is umckaloabo, which originates from *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt. Whereas *Pelargonium* species represent very popular ornamental plants in Europe, little was known of the medicinal practice with pelargoniums in folk medicine in areas of southern Africa. Infusion of the roots of *P. sidoides* and *P. reniforme* is used to treat coughs, chest problems including tuberculosis and gastrointestinal disorders such as diarrhea and dysentery. In addition, umckaloabo is claimed to provide a cure for hepatic disorders and dysmenorrhea. The aerial parts of these *Pelargonium* species are employed as wound healing agents (Kolodziej, 2000).

The drug was introduced to England and Europe by the British mechanic Charles Henry Stevens in the 19th century for the treatment of tuberculosis. Stevens believed that he recovered form tuberculosis by the administration of a decoction of umckaloabo prepared by a traditional healer (Helmstädter, 1996).

The true botanical nature of umckaloabo was debated for many years. By comparative botanical as well as chromatographic studies it could be proved that umckaloabo must have originated from *Pelargonium* species i.e. *Pelargonium sidoides* or *Pelargonium reniforme*. Species *Pelargonium* are very similar and have been much confused in the past. The existence of gradual variation between both species contributed to general problems of taxonomic classification, as reflected in the past by numerous revisions of the Linneaen taxonomic system (Kolodziej, 2002) (van Wyk, 2008). The use of both species is also accepted by the European Pharmacopoeia monograph describing *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt in one monograph without defining specific parameters for differentiation (Ph. Eur. 6.0, 2008).

The two species can be distinguished by the shape of the leaves, the colour of the flowers and the pollen. *P. sidoides* is characterized by dark red to almost black flowers, cordate-shaped leaves and yellowish pollen, while the zygomorphosous flower heads of *P. reniforme* are magenta red with two distinctive stripes on the upper two petals, the pollen is whitish-green, and the reniform leaves represent a characteristic feature that is reflected by its botanical name "reniforme". Differentiation of the roots is more difficult and refers to the colour of the root wood and the thickness of the phellem. In *P. sidoides* the root wood is dark brown, while in *P. reniforme* it is markedly lighter or appears yellow. The geographical range of distribution of two species also differs. *P. reniforme* mainly occurs in coastal regions in the Eastern Cape of southern Africa, while *P. sidoides* are predominantly found over large parts of the interior of southern Africa, but also occur in coastal mountain ranges up to 2300 m (Bladt and Wagner, 2007) (Brendler and van Wyk, 2008).

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

- Herbal substance(s)

Dried underground organs of *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt. (Ph. Eur. 6.0, 2008)
The scientific monographs (Comission E, ESCOP and WHO monographs) do not include sections on *Pelargonium sidoides*.

- Herbal preparation(s)

Well-established use:

In the majority of clinical trials, the study medication was the aqueous ethanolic (11% m/m) extract of the roots of *P. sidoides* (DER 1:8-10) in solution forms. Two trials examined the effect of *Pelargonium* preparation in tablet form (11% (m/m) ethanol dried extract of *P. sidoides* radix) (Schulz, 2008a) (Kamin et al., 2010a).
According to information provided by the National Competent Authorities (see section 1.2) *Pelargonium* preparations with ethanol (50% m/m) as extraction solvent are also available on the European market. There are no data about the chemical and pharmacological equivalence of 11% m/m and 50% m/m ethanol extract of *Pelargonium sidoides*.

- 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.

Not applicable.

- Constituents

Coumarins. Are formed from cis-hydroxycinnamic acid by lactonization and have limited distribution in the plant kingdom. They have been found in about 150 species, mainly in the plant families *Apiaceae*, *Rutaceae*, *Asteracae*. The characteristic constituents of *Pelargonium* species include a remarkable series of simple coumarins as regards the high degree of aromatic functionalization including hydroxyl and methoxyl groups (Kayser and Kolodziej, 1995). Apart from the widely distributed di-substituted scopoletin, all the coumarins possess tri- and tetra substituted oxygenation patterns on the aromatic nucleus. Amongst these, 5,6,7- or 6,7,8-trihydroxycoumarin and 8-hydroxy-5,6,7-trimethoxycoumarin represent the metabolites of the above class of secondary products (Table 1.). Such combined oxygenation patterns are very rare in plant kingdom, but apparently typical for the genus *Pelargonium* (Kolodziej, 2000).

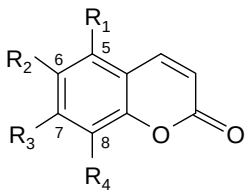
6,7-dihydroxy-derivative
scopoletin
5,6,7-trisubstituted derivatives
umckalin
5,6,7-trimethoxycoumarin
6,7,8-trioxygenated derivatives
6,8-dihydroxy-7-methoxycoumarine
fraxetin
5,6,7,8-tetrasubstituted derivatives
6,8-dihydoxy-5,7-dimethoxycoumarine
artelin
coumarin glycoside
umckalin-7-β-glucoside
coumarin sulfate
5,6-dimethoxycoumarin-7-sulfate

Table 1. Typical coumarin compounds of *P. sidoides* (Kolodziej, 2007)

Compositional studies of the roots of two species provided a similar picture of a broad metabolic profile, reflecting a close botanical relationship between them. In spite of the similar patterns of coumarins, a distinguishing feature appeared to be the presence of a 5,6-dimethoxy arrangement within the group of 5,6,7-trioxygenated members of *P. sidoides* (umckalin, 5,6,7-trimethoxycoumarin) and an unsubstituted 6-hydroxyl function in that of *P. reniforme* (fraxinol, isofraxetin) (Latte et al., 2000) (Kolodziej, 2002) (Table 2.). Another discriminating chemical character was the distinct occurrence of coumarin sulfates and coumarin glycosides in *P. sidoides* (Kolodziej et al., 2002) (Kolodziej, 2007). These coumarin derivatives and umckalin are known to be useful marker compounds for *P. sidoides*, as they appear to be absent in *P. reniforme* (Brendler and van Wyk, 2008). In addition, there is much divergence in concentration, with generally significantly higher yields of coumarins in *P. sidoides*. The total coumarin content of the roots of *P. sidoides* is approximately 0.05% related to dry weight, with umckalin amounting for about 40% of total coumarin content (Latte et al., 2000).

A rapid TLC method, a HPLC-fingerprint analysis and HPLC-quantitative estimation were developed for coumarins containing the roots of *Pelargonium* species by Bladt and Wagner (1988). Franco and de Oliveira (2010) presented a new, validated HPLC method for quality control of plant extracts and phytopharmaceuticals containing *P. sidoides*, using umckalin as chemical markers.

White et al. (2008) drew the attention to the uncontrolled harvest of at least 20 tones of *P. reniforme* and *P. sidoides* in the Eastern Cape in 2002. These facts raised the need for development of sustainable harvesting practice and methods for the effective cultivation of this species. The authors investigated by HPLC the variation in the concentration of umckalin within and between plants populations collected from different geographical locations and monitored the effect of various cultivation techniques including the manipulation of soil water content and pH level. The final conclusion was that the greenhouse-cultivated plants showed equivalent umckalin concentrations and circa six-times greater growth rates than plants in wild-harvest experiments.



	R^1	R^2	R^3	R^4	Occurrence
scopoletin*	H	OCH_3	OH	H	Both species
6,7,8-trihydroxycoumarin*	H	OH	OH	OH	
8-hydroxy-5,6,7-trimethoxycoumarin*	OCH_3	OCH_3	OCH_3	OH	
artelin*	OCH_3	OCH_3	OCH_3	OCH_3	*P. sidoides*
umckalin*	OCH_3	OCH_3	OH	H	
5,6,7-trimethoxycoumarin*	OCH_3	OCH_3	OCH_3	H	
fraxetin	H	OCH_3	OH	OH	
fraxinol	OCH_3	OH	OCH_3	H	*P. reniforme*
isofraxetin	OH	OH	OCH_3	H	

Table 2. Coumarin patterns of *Pelargonium* species
* Compounds were indentified in EPs® 7630

Other constituents. Structural examination of root metabolites of *Pelargonium* species led to the characterization of other various compounds including phenolic acids, flavonoids, flavan-3-ols with

associated proanthocyanidins and one phytosterol. With the exception of gallic acid and its methyl ester, the majority of these metabolites have been found in relatively low yields. In contrast, the oligomeric and polymeric proanthocyanidins occur in high concentration, with catechin and gallocatechin entities, as dominating extender units (Gödecke et al., 2005) (Kolodziej, 2002). The heterogeneity of metabolites in *P. reniforme* root extract was further demonstrated by the characterization of an unprecedented diterpene ester, designated as reniformin (Latte et al., 2007).

According to European Pharmacopoeia, *Pelargonium* root has to contain not less than 2.0% of tannins, expressed as pyrogallol. The identification method of European Pharmacopoeia is thin layer chromatography of methanol root extract, but HPLC fingerprint analysis of *Pelargonium* extract was already achieved (Bladt and Wagner, 1988). Schnitzler et al. (2008) analyzed the compounds of aqueous root extract of *P. sidoides* by LC-MS spectroscopy. Predominant coumarins, simple phenolic structure as well as flavonoid and catechin derivatives were identified as major constituents in *Pelargonium* extract (Figure 1.).

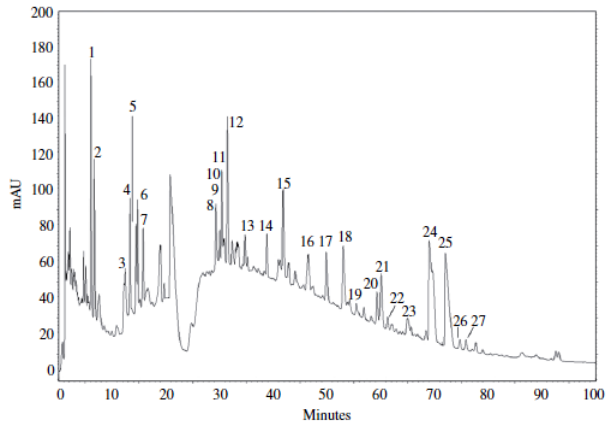


Figure 1. HPLC chromatogram of an aqueous *P. sidoides* extract at 260 nm (Schnitzler et al., 2008)

(Assignment: 3- glucogallin, 8- fraxetin-7-O-glucoside, 11- catechin, 12- dihydroxy-coumarin-sulfate, 15- fraxetinsulfate, 16- monohydroxy-dimethoxycoumarin, 19,22- dihydroxy-dimethoxycoumarin, 23- dihydrokaemferol, 25- umckalin)

The total mineral content of EPs® 7630 was found to be 10-12%. The cations were detected by ICP-MS: potassium (4%), sodium (1.2%) and magnesium (0.4%). Anions were quantified by ion chromatography giving sulfate (4.5%), phosphate (2%) and chloride (1%) (Schötz et al., 2008).

Quantified extract of *P. sidoides*. EPs® 7630 is a special aqueous ethanolic (11% m/m) extract of *P. sidoides* roots. The fundamental structural studies on the *Pelargonium* species were recently extended to this medicinal product. Schötz et al. (2008) give a detailed account of the constituents of EPs® 7630. The extraction method yields a specific range of constituents markedly different from those obtained from extraction with non-polar solvents. Six main groups of compounds can be found in EPs® 7630: purine derivatives (2%), coumarins (2%), peptides (10%), carbohydrates (12%), minerals (12%) and oligomeric prodelphinidines (40%). The identified coumarin pattern is strongly reminiscent to that of *P. sidoides* (Kolodziej, 2007). A remarkable feature is that predominant amounts of coumarins occur as their sulfated derivatives. In addition, the stability for sulfated coumarins appears to be enhanced in the extract, whereas these compounds decompose rather quickly when they are isolated. A considerable proportion of high molecular weight proanthocyanidins was found in EPs® 7630. A diverse set of epigallo-and gallocatechin based oligomers were isolated from EPs® 7630, which are connected

by A and B-type bonds. Additionally, two series of monosubstituted oligomers, sulfates and aminoconjugates were detected by mass spectroscopy (Schötz and Nödler, 2007).

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

Austria:

Traditional herbal medicinal products

Preparations:
1-2) Extract (1:8-10), extraction solvent: ethanol 11% m/m

Pharmaceutical form:
1) Film-coated tablet
2) Oral liquid

Posology:
all for oral use
1) > 12 y: 3 x daily 1 containing 20 mg extract
2) 1-5 y: 3 x daily 10 drops
   6-12 y: 3 x daily 20 drops
   > 12 y: 3 x daily 30 drops
   10 g (= 9.75 ml) liquid contain 8.0 g extract

Indication:
1) Common cold
2) Common cold

Legal status:
1-2) Registered traditional herbal medicinal products

Since when is on the market:
1) 2009
2) 2007

Belgium:

Traditional herbal medicinal products

Preparations:
1) Pelargonium sidoides roots, liquid extract EtOH 11% (m/m) DER 1:8-10
2) Pelargonium sidoides roots, dried extract EtOH 11% (m/m) DER 1:8-10

Pharmaceutical form:
1) Oral solution: 8.0 g extract per 10 g solution
2) Tablets: 20 mg extract per tablet
   Syrup 0.25 g extract per 100 g syrup

Posology:
1) Adults & children > 12 y: 30 drops, 3 times daily
   Children 6-12 y: 20 drops, 3 times daily
   Children 1-5 y: 10 drops, 3 times daily
Drops to be taken preferably morning, noon and evening with some liquid
Average duration of administration is 7 days. Continue the treatment for some days when symptoms

are decreasing.
Maximal duration: 3 weeks

2) TABLETS
Adults & children > 12 y: 1 tablet 3 times daily (morning, noon, evening)
Children 6-12 y: 1 tablet, 2 times daily (morning, evening)
Tablets to be taken with some liquid; do not chew

3) SYRUP
Adults & children > 12 y: 7.5 ml, 3 times daily
Children 6-12 y: 5 ml, 3 times daily
Children 1-5 y: 2.5 ml, 3 times daily
Average duration of administration is 7 days. Continue the treatment for some days when symptoms are decreasing.
Maximal duration: 3 weeks

Indication:
1) Common cold, exclusively based on traditional use
2) Common cold, exclusively based on traditional use

Legal status:
1) Registered traditional herbal medicinal product
2) Registered traditional herbal medicinal product

Since when is on the market:
1) 2009
2) 2009

Czech Republic:

Herbal medicinal product with well-established use

Preparations:
1) Pelargonii sidoides extractum fluidum (1:8–10), extraction solvent ethanol 11% (m/m)

Pharmaceutical form:
1) Solution, oral drops

Posology:
1) 1 g = 20 drops of the medicinal product contains 800 mg of the extract

Adults and adolescents over 12 years: 30 drops 3 times daily
Children 6–12 y: 20 drops 3 times daily
Children 1–5 y: 10 drops 3 times daily

Duration of use 7–10 days

Indication:
1) Symptomatic treatment of acute bronchitis not requiring antibiotic therapy

Legal status:
1) Authorized herbal medicinal product

Since when is on the market:
1) 2008

Germany:

Herbal medicinal products with well-established use

Preparations:
1-9) Extract (1:8-10), extraction solvent: ethanol 11% m/m

Pharmaceutical form:
1-3) Film-coated tablet
4-9) Oral liquid

Posology:
all for oral use
1-3) > 12 y: 3 x daily 1 containing 20 mg extract
4-9) 1-5 y: 3 x daily 10 drops
6-12 y: 3 x daily 20 drops
> 12 y: 3 x daily 30 drops
10 g (= 9.75 ml) liquid contain 8.0 g extract

Indication:
1-3) For symptomatic treatment of acute bronchitis
4-9) Acute bronchitis

Legal status:
1-9) authorized herbal medicinal products

Since when is on the market:
1-3) 2009
4) at least since 1976
5-9) 2006

Hungary:

Traditional herbal medicinal products

Preparations:
1) 10.0 g of oral solution containing 8,0 g of Pelargonium sidoides radix extract (1:8-10) (EPs® 7630)
Extraction solvent: 11 % ethanol (m/m)

Pharmaceutical form:
1) Oral solution

Posology:
1) Adults and adolescent above 12 y: 3 x 30 drops daily
Children between 6-12 yrs: 3 x 20 drops daily

Indication:
1) Acute infections of upper airways, such as symptomatic treatment of common cold

Legal status:
1) Registered traditional herbal medicinal product

Since when is on the market:
1) 2009

Italy:

1) *Pelargonium sidoides*, radix, liquid extract (1-8:10, ethanol 11% w/w) (EPs® 7630) 80% oral drops, solution (multiple application)

2) *Pelargonium sidoides*, root dry extract (1-8:10, ethanol 11% w/w) (EPs® 7630) 20 mg film coated tablets (multiple application)

Therapeutic indication for both: THMP for the relief of common cold, exclusively based on long-standing use

Slovakia:

Herbal medicinal product with well-established use

Preparations:
1) 10.0 g (= 9.75 ml) of oral solution containing 8.0 g of Pelargonium sidoides radix extract (1:8-10) (EPs® 7630), extraction solvent: 11% ethanol (m/m)

Pharmaceutical form:
1) Oral solution

Posology:
1) Adults and adolescent above 12 y: 30 drops 3 times daily
   Children between 6-12 y: 20 drops 3 times daily
   Children between 1-5 y: 10 drops 3 times daily

Indication:
1) Acute infections of upper airways.

Legal status:
1) Authorized herbal medicinal product

Since when is on the market:
1) 2007

Spain:

Traditional herbal medicinal products

Preparations:
1) 10 g (= 9.75 ml) of oral solution contains 8.0 g extract from the roots of *Pelargonium sidoides* DC (1:8–10; 11% ethanol (m/m)), 1 ml (approximately 20 drops)
2) 20 mg of dry extract from the roots of *Pelargonium sidoides* DC (1:8–10; 11% ethanol (m/m))/tablet

Pharmaceutical form:
1) Solution, oral drops
2) Tablets

Posology:
1) Adults and adolescents: 30 drops 3 times daily
   Children 6-12 y: 20 drops 3 times daily
2) Adults and children over 12 y: 1 tablet 3 times daily

Indication:
1) Traditional herbal medicinal product used to relieve the symptoms of common cold, based on traditional use only.
2) Traditional herbal medicinal product used to relieve the symptoms of common cold, based on traditional use only.

Legal status:
1) Registered traditional herbal medicinal product
2) registered traditional herbal medicinal product

Since when is on the market:
1) 2009
2) 2009

Sweden:

Traditional herbal medicinal products

Preparations:
1) Root, dry liquid extract, extraction solvent: ethanol 11% (m/m). DERgenuine 1:8-10 (liquid extract), DER 4-25:1 (dried liquid extract), DERmanufacturing 0.7-4.5:1.
2) Root, liquid extract, extraction solvent: ethanol 11% (m/m). DERgenuine 1:8-10

Pharmaceutical form:
1) Film-coated tablet
2) Oral drops, solution

Posology:
1) Adults and adolescents over 12 y: 1 tablet 3 times daily
   Children between age 6 and 12 y: 1 tablet 2 times daily
   Not recommended to children under age of 6.
2) Adults and adolescents over 12 y: 30 drops 3 times daily
   Children between age 6 and 12: 20 drops 3 times daily
   Not recommended to children under age of 6.
   1 ml is equivalent to 20 drops.

Indication:
1) Traditional herbal medicinal product for symptomatic relief of the common cold
2) Traditional herbal medicinal product for symptomatic relief of the common cold

Legal status:
1) Registered traditional herbal medicinal product
2) Registered traditional herbal medicinal product

Since when is on the market:
1) 2009-05-11
2) 2009-05-11

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Two registered products
Belgium	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	Two products
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	One product
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Nine products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One product
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	One product
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Two products
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Two products

Member State	Regulatory Status				Comments (not mandatory field)
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response

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

Databases SciFinder, Science Direct, Web of Science and PubMed were searched using the terms [*Pelargonium*], [EPs® 7630] and [coumarin]. Handbooks and textbooks were also used.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Pelargonium sidoides is native to South Africa and is used against several diseases by traditional healers. The Englishmen Charles Henry Stevens discovered the crude herbal drugs when he went to South Africa in 1897 on his doctor's advice, in order to cure his tuberculosis in the clear mountain air. Over there he met a Zulu medicine man, who treated him with a boiled root preparation. Three months later he felt well and considered himself as cured. After returning to the UK, he set up a company to prepare and sell his remedy under the name of "Stevens' Consumption Cure". The name umckaloabo was used by Stevens to describe the mysterious root material and this term was distributed all over the world. The Zulu words for lung disease symptoms and breast pain are the origins of the name umckaloabo.

In the early 1900s, Stevens' Consumption Cure was very popular remedy against tuberculosis in England. In 1909, the British Medical Association (BMA) published a book with the title "Secret Remedies: What they cost and what they contain". In that book Stevens was accused of quackery, as the powder showed a microscopic similarity to other tannin drugs, such as rhatany root. He took action for libel against BMA, but the jury decided in favor of BMA and he was ordered to pay 2000 pounds of legal cost.

After the First World War, Stevens continued to promote umckaloabo. In 1920, the French-Swiss physician A. Sechehaye started to treat TB patients with Stevens' Cure. During 9 years, he documented the treatment of around 800 patients and reported successful cases to the Medical Society of Geneva. He also investigated the antibacterial action of the remedy in laboratory surroundings. Sechehaye came to the conclusion that in many TB cases, with the exception of acute, malignant and complicated cases the drug could be seen to be efficacious. In 1933, the physician Bojanowski reported about five cases of successful treatment of tuberculosis with *Pelargonium* preparations in Germany (Helmstädter, 1996), (Taylor et al., 2005), (Bladt and Wagner, 2007), (Brendler and van Wyk, 2008).

At first, Stevens' Cure was a powder of crude drug suspended in water, but in the early years in England the remedy was sold as liquid, containing alcohol, glycerine and a drug decoction. In Switzerland, a fluid extract was probably the predominant dosage form, while in Germany the drug was sold as powder, extract or tincture (Helmstädter, 1996).

Despite the repeated attempts, the remedy was unidentified until 1977, when S. Bladt, at the University of Munich, used ethnobotanical, comparative botanical and chromatographic techniques to show that the roots originated from species *Geraniaceae*, *Pelargonium sidoides* and/or *P. reniforme* (Bladt and Wagner, 1977). At this point, the drug received renewed interest and pharmacological research was initiated.

Marketing of the remedy as a treatment for bronchitis and symptoms of common cold already started in the 1970's. Umckaloabo received a full market authorization by the German drug regulatory agency in 2005. Until this time, a tincture 1+10 from *P. sidoides*/*reniforme* was used, from 2005 the ingredients changed to a solution of *P. sidoides* (Brendler and van Wyk, 2008).
The monograph of *Pelargonium sidoides*/*reniforme* root (Pelargonii radix) was introduced into European Pharmacopoeia in 2007.
Outside Europe, various liquid and solid preparations are available as herbal supplements especially in North America and Mexico.

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

The information about therapeutic indications of *Pelargonium* preparation is available from clinical trials and manufacture. The efficacy of *Pelargonium* extract was examined in patients with acute bronchitis, acute sinusitis, common cold and tonsillopharynhitis. The producers suggest the internal use of *Pelargonium* extract in case of acute infection of upper airways, common cold and symptomatic treatment of acute bronchitis not requiring antibiotic therapy.

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

The clinical studies and the product information provide guidance for the dosage of *Pelargonium* preparations. In the majority of clinical trials adult patients took 30 drops of liquid preparation three times daily. The duration of application was usually 7 days. 10 g of liquid preparation usually contains 8.0 g of 11% m/m ethanol extract of *P. sidoides* radix (DER 1:8-10).

The clinical studies including children suggested 3 x 5 drops of liquid preparation for children under 2 years of age, 3 x 10 drops for children between 2-6 years of age and 3 x 20 drops for children between 6-12 years of age. In other clinical trials children between 1-6 years of age were instructed to take 3 x 10 drops of liquid preparation (Table 3-7). According to package leaflets, 3 x 30 drops of solution or 3 x 1 tablets are prescribed for adults and 3 x 20 drops or 2 x 1 tablets for children between 6-12 years of age. One tablet contains 20 mg of *Pelargonium sidoides* ethanolic extract, but there is no information about the equivalence of liquid solution and tablet forms.

According to the market overview, one extract (DER 1:8-10, extraction solvent: ethanol 11% m/m) of Pelargonii radix has been on the market for more than 30 years with the indication acute bronchitis (see product no. 4 in the German market overview, section 1.2). However, this indication needs medical diagnosis and supervision. Based on other traditional herbal medicinal products with the same composition in other member states, the following indication was accepted: symptomatic treatment of common cold.

3. Non-Clinical Data

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

Antibacterial activity

Kayser and Kolodziej (1997) investigated the antibacterial activity of extracts and isolated compounds (scopoletin, umckalin, 5,6,7-trimethoxycoumarin, 6,8-dihydroxy-5-7-dimethoxycoumarin, (+)-catechin, gallic acid and its methyl ester) of *P. sidoides* and *P. reniforme* against 8 microorganisms, including Gram-positive (*Staphylococcus aureus*, *Streptococcus pneumoniae* and beta-hemolytic *Streptococcus* 1451) and Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*) using an agar dilution method. These pathogens are primarily responsible for numerous respiratory tract infections. The crude *Pelargonium* extracts were found to be moderately active against the tested bacteria. Apart from (+)-catechin, all the tested compounds exhibited moderate antibacterial activity with MICs ranging from 220-2000 µg/mL. (Penicillin G and erythromycin were used as reference agents. The MIC value of penicillin G was 5-166 µg/mL and the MIC value of erythromycin was 2-125 µg/mL under the same experimental conditions). The most potent candidates with MICs of 200-500 µg/mL were umckalin and 6,8-dihydroxy-5,7-dimethoxycoumarin, which are present in considerable amounts in the aqueous phase of *Pelargonium* species. The aqueous phase showed the highest activity from the tested extracts.

Acetone and methanol extracts of *P. sidoides* were investigated for antimicrobial activity against 10 bacterial (*B. cereus*, *S. epidermidis*, *S. aureus*, *M. kristinae*, *S. pyogenes*, *E. coli*, *S. pooni*, *S. marcescens*, *P. aeruginosa*, *K. pneumoniae*) and 5 fungal species (*A. flavus*, *A. niger*, *F. oxysporium*, *M. hiemalis*, *P. notatum*) by Lewu et al. (2006a). With the exception of *Staphylococcus epidermidis*, extracts obtained from both solvents demonstrated significant activity against all the Gram-positive bacteria tested in this study. The MIC ranged from 1 to 5 mg/ml except the acetone extract against *Klebsiella pneumoniae* where the value was 10 mg/ml. Three Gram-negative bacteria, *Escherichia coli*, *Serratia marescens* and *Pseudomonas aeruginosa* were not inhibited by any of the extracts at the highest concentration (10 mg/ml) tested. The extracts also showed appreciable inhibitory activity against all the fungal species tested.

A comparative study of antibacterial activity of the shoots and the roots of *P. sidoides* was performed by Lewu et al. (2006b). There was no significant difference between the MIC values of extracts from both parts. Furthermore, the similar bioactivity of plant materials collected from different populations was found. With the exception of *Staphylococcus epidermidus* and *Micrococcus kristinae* the extracts from both the roots and the leaves showed activity against all the Gram-positive bacteria tested with MIC ranging from 1.0 to 7.5 mg/ml. Gram-negative bacteria were not, or only slightly inhibited.

Similar moderate antibacterial activities were evident for EPs® 7630 (MIC values: *Klebisella pneumoniae* 13.8 mg/nl, *Escherichia coli* >13.8 mg/ml, *Pseudomonas aeruginosa* >13.8 mg/ml, *Proteus mirabilis* 3.3 mg/ml). This extract was also effective against multiresistant strains of *S. aureus* with MICs of 3.3 mg/mL (Kolodziej et al., 2003).
Nevertheless, the demonstrated direct antibacterial activity cannot adequately explain the documented clinical efficacy of *Pelargonium*-containing herbal medicines in the treatment of respiratory tract infections. The anti-infectious capabilities may also be due to indirect effects, e.g. interaction between pathogens and epithelial cells (Kolodziej et al., 2003) (Kolodziej and Kiderlen, 2007).

A synergistic indirect antibacterial effect of EPs® 7630 in group A-streptococci (GAS) was established through inhibition of bacterial adhesion to human epithelial cells (HEp-2) as well as induction of bacterial adhesion to buccal epithelial cells (BEC) (Brendler and van Wyk, 2008).

Conrad et al. (2007a, b) investigated the impact of a therapeutically relevant concentration of 1-30 µg/mL EPs® 7630 on the activity of human peripherial blood phagocytes (PBP) and on host-bacteria interaction *in vitro*. A flow cytometric assay, microbiological assay and penicillin/gentamicin-protection assay were used to determine phagocytosis, oxidative burst and adhesion of GAS on human HEp-2 and BEC, intracellular killing and GAS invasion of HEp-2 cells. The number of phagocytosing PBP and intracellular killing were increased by EPs® 7630 in a concentration dependent manner. EPs® 7630 reduced GAS adhesion to HEp-2 cells significantly, but increased GAS adhesion to BEC. The authors concluded that EPs® 7630 can protect the upper respiratory tract from bacterial colonization by reducing bacterial adhesion to epithelial cells. On the other hand, the attachment of bacteria to BEC is enhanced, so that pathogens are released during coughing and eventually inactivated by being swallowed (Conrad and Frank, 2008). Further investigations by Dorfmüller et al. (2005) and Brendler and van Wyk (2008) complemented these findings.

Wittschier et al. (2007) used *Helicobacter pylori*, as a model microorganism to investigate the effect of EPs® 7630 on microbial adhesion by fluorescent technique. The extract showed antiadhesive activity in a dose-dependent manner in the range 0.01-10 mg/ml, but a direct cytotoxic effect against *H. pylori* could not be established. Beil and Kilian (2007) also showed that EPs® 7630 interferes with *H. pylori* growth and adhesion to gastric epithelial cells.

Antimycobacterial properties

The traditional use of *Pelargonium* extract against tuberculosis prompted to investigate the antimycobacterial effect of *Pelargonium* species.
The extract of *P. sidoides* showed inhibitory activity against *Mycobacterium tuberculosis* in a radiorespiromertric bioassay at a sample concentration of 12.5 µg/mL, while that of *P. reniforme* was inactive. None of the isolated simple phenolic compounds and coumarins exhibited any antimycobacterial activity under these conditions. In the microdilution Alamar Blue assay, the extract of *P. sidoides* was moderately active against *M. tuberculosis* with a MIC of 100 µg/mL in comparison with the clinically used drug rifampicin (MIC of 0.06 µg/mL) (Kolodziej et al., 2003).

The antimycobacterial activity of hexane extracts of roots of *P. sidoides* and *P. reniforme* was investigated by Seidel and Taylor (2004) against rapidly growing mycobacterium – *M. aurum*, *M. smegmatis*. Several mono- and diunsaturated fatty acids were found as active compounds by bioassay-guided fractionation. Oleic acid and linoleic acid were the most active with MICs of 2 mg/L; isoniazid used as standard had a MIC of 0.06-1 mg/L.

Mativandlela et al. (2006) investigated various extracts and isolated compounds from the roots of *Pelargonium* species with regard to their antibacterial especially their antimycobacterial activities. Limited activity (MICs of ~5000 mg/L, compared to MIC of 0.2 mg/L of rifampicin) against *Mycobacterium tuberculosis* could be shown for acetone, chloroform and ethanol extracts of *P. reniforme*. None of the isolated compounds showed any activity against *M. tuberculosis*.

The aqueous acetone extracts of both root material and aerial parts as well as fractions of *P. sidoides* showed negligible antimycobacterial activities against nonpathogenic *Mycobacterium aurum* and *M. smegmatis* in a microdilution assay, with MICs of >1024 µg/mL. Inhibition of growth was measured by MTT assays, using ethambutol as a positive control (MIC 2 µg/mL) (Kolodziej and Kiderlen, 2007).

The butanol root extract of *P. sidoides* was found have inhibitory activity against *M. tuberculosis* at a concentration of 2500 µg/mL. The isolated compounds (flavonoids and coumarins) did not show activity against *M. tuberculosis* (Patience et al., 2007).

The aqueous extract of the root of *P. reniforme* stimulated the macrophage killing of the intracellular pathogen *M. tuberculosis*. Kim et al. (2009) identified gallic acid and methyl gallate as the most bioactive components of the highly effective water fraction by bioassay-guided fractionation.

Immunomodulatory properties

To assess the immunostimulating activity of *P. sidoides* and its constituents, functional bioassays including an *in vitro* model for infection with *Leishmania* parasites, a fibroblast-virus protection assays (IFN activity), a fibroblast-lysis assay (TNF activity), a biochemical assay for nitric oxides, as well as gene expression analyses were employed.

Kayser et al. (2001) performed an experiment to assess the immune modulatory properties of extract and constituents of *P. sidoides* in various bioassays. An *in vitro* model for visceral leishmaniasis was selected in which murine macrophages are infected with the intracellular protozoon *Leishmania donovani*. None of the tested samples (methanol, petrol ether, ethyl-acetate and n-butanol extract of *P. sidoides* root and pure compounds: gallic acid, gallic acid methyl ester, (+)-catechin, 6-hydroxy-7-methyoxycoumarin, umckalin, 5,6,7-trimethyoxycoumarin and 6,8-dihydroxy-5,7-dimethyoxycoumarin) revealed significant activity against extracellular, promastigote *Leishmania donovani*. However, all the *Pelargonium* extracts, gallic acid and its methyl ester significantly reduced the intracellular survival of *L. donovani*. The samples exhibited no or negligible host cell cytotoxicity. These findings indicated that the samples acted indirectly against *Leshmania* parasites, possibly activating macrophage functions. Macrophage activation was confirmed by detection of tumour necrosis factor (TNF-α) and inorganic nitric oxides (iNO) in supernatants of sample-treated cell cultures. Gallic acid and its methyl ester were identified as prominent immunomodulatory principles for *P. sidoides* by bioassay-guided fractionation.

Thäle et al. (2008) concluded that EPs® 7630 significantly increased release of NO, production of intra- and extracellular IL-1, IL-12, and TNF-α, thereby reducing the survival rate of intracellular parasites. The bone marrow-derived macrophages experimentally infected with intracellular bacteria *Listeria monocytogenes* were incubated with EPs® 7630 (1-30 µg/mL). Compared with non-infected cells, the effects were more pronounced.

Kolodziej et al. (2003) observed that EPs® 7630 possessed TNF-inducing potency and interferon-like activity in supernatants of sample-activated bone marrow-derived macrophages in several functional assays. In addition, EPs® 7630 stimulated the synthesis of IFN-β in human MG-63 osteosarcoma cells. Stimulation of RAW 264.7 cells with gallic acid, as characteristic compounds of EPs® 7630 resulted in gene expression of iNOS and TNF-α transcripts.

Koch et al. (2002) also confirmed that EPs® 7630 increased the IFN-β prodution in MG-63 cells preincubated with the preparation. Enhancement of cytotoxicity mediated by natural killer cells was also found.

Confirmatory evidence of non-specific immunmodulatory activity of EPs® 7630 as provided by functional assays was available from gene expression analyses. EPs® 7630 and simple phenols, flavan-3-ols, proanthocyanidins and hydrolysable tannins were studied for gene expressions (iNOS, IL-1, IL-10, IL-12, IL-18, TNF-α, IFN-α/γ) by RT-PCR. All tested samples were capable of enhancing the iNOS and cytokine mRNA levels in infected cells when compared with those in non-infected conditions (Kolodziej et al., 2005).

Trun et al. (2006) carried out gene expression analysis for the iNOS and the cytokines IL-1, IL-12, IL-18, TNF-α, IFN-α and IFN-γ in non-infected and in *Leishmania major*-infected RAW 264.7 cells. EPs® 7630 induced strongly the gene expression of iNOS and a series of cytokine mRNAs in infected cells. Similar profiles were obtained for the methanol-insoluble fraction and gallic acid. The methanol-soluble fraction and umckalin did not show any significant gene-inducing capabilities. Other studies also confirmed that there was difference in the gene expression response of infected macrophages when compared to that of non-infected cells (Kolodziej and Kiderlen, 2007).

Koch and Wohn (2007) evaluated the effects of EPs® 7630 on release of antimicrobial peptides from neutrophils using ELISA kits. The cytoplasmatic granules of neutrophil granulocytes contain a variety of antimicrobial proteins - bactericidal/permeability-increasing protein (BPI), human neutophil peptides (HNP) and defensins-, which possess antimicrobial as well as chemotactic, immunomodulating and wound-healing activity. EPs® 7630 concentration-dependently increased the release of HNP 1-3 and BPI.

Other anti-infective activity- antifungal, antiviral and mucolytic effect

In a microbiological killing assay, human peripheral blood phagocytes were found to significantly reduce the number of surviving *Candida albicans* organisms, pretreated with EPs® 7630. Since the extract did not show direct antifungal activity in the test system, the intracellular destruction of the test organism was concluded to be due to enhanced phagocyte killing activity induced by EPs® 7630 (Conrad et al., 2007a).

Schnitzler et al. (2008) examined the antiviral effect of aqueous root extract of *P. sidoides* in cell culture. Concentration-dependent antiviral activity against herpes simplex virus type 1 (HSV 1) and herpes simplex virus type 2 (HSV 2) could be demonstrated for this extract. Both viruses were significantly inhibited when pre-treated with the plant extract or when the extract was added during the adsorption phase, whereas acyclovir, the commercial antiviral drug demonstrated activity only intracellularly during replication of HSV. These results indicated that *P. sidoides* extract affected the virus before penetration into the host cell and reveals a different mode of action when compared to the classical drug acyclovir.

Nöldner and Schötz (2007) studied the inhibition of sickness behavior (anorexia, depressed activity, listlessness and malaise) by EPs® 7630 and its different fractions separated by ultrafiltration in an animal model. In laboratory animals, the sickness behaviour was induced by administration of cytokine-inducer. Oral administration of EPs® 7630 and the high molecular weight fraction (>30 kDa) antagonised the above-mentioned effects in a dose-dependent manner.

Neugebauer et al. (2005) demonstrated that EPs® 7630 significantly and dose-dependently increased the ciliary beat frequency *in vitro*. According to authors, these results suggest the local application of EPs® 7630 close to nasal mucosa, but it could be limited by a moderate astringent effect of tannin compounds of extract.

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

Absorption, metabolism, elimination

There are no available data about pharmacokinetic parameters of *Pelargonium* extract; the relevant information about constituents is presented.

The pharmacokinetics of coumarin, the basic compound of coumarin group has been studied in a number of species, including humans. These human studies demonstrated that coumarin was

completely absorbed from the gastrointestinal tract after oral administration and extensively metabolized by the liver in the first pass, with only between 2 and 6% reaching the systematic circulation intact. In the majority of human subjects studied, coumarin is extensively metabolized to 7-hydroxycoumarin by hepatic CYP2A6. After administration of coumarin, 68-92% of the dose was 7-hydroxycoumarin in urine as glucuronide and sulfate conjugates. While 7-hydroxylation is the main way of coumarin metabolism in humans, the major pathway in most rodents is by 3,4-epoxidation resulting in the formation of ring opened metabolites including o-HPA, o-HPPA (Figure 2). Several studies examined the toxic effect of coumarin in rats by the formation of these metabolites. A deficiency in the 7-hydroxylation pathway has been observed in some individuals, which appears to be related to a genetic polymorphism in CYP2A6. The limited *in vitro* and *in vivo* data available suggest that such deficient individuals will metabolize coumarin by the 3,4-epoxidation and possibly other pathways leading to formation of toxic o-HPAA (Egan et al., 1990) (Lake, 1999).

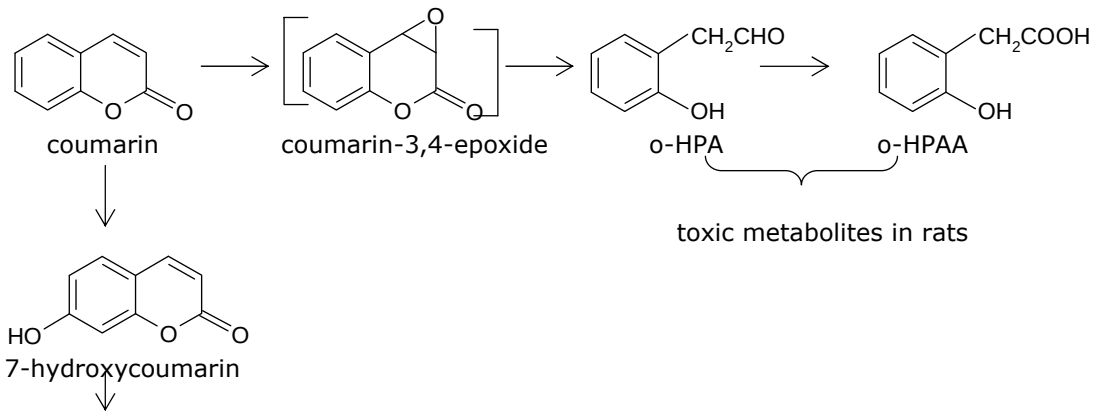


Figure 2. Some pathways of coumarin metabolism (o-HPA = o-hydroxyphenylacetaldehyde; o-HPAA = o-hydroxyphenylpropionic acid) (Lake, 1999)

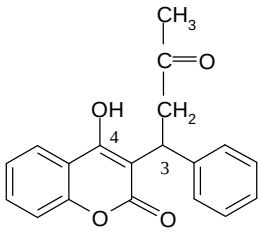
According to human data the elimination of coumarin from the systematic circulation is rapid. The *in vivo* and human studies concluded that there are important quantitative differences between species in the routes of elimination of coumarin metabolites. The majority of studies demonstrated a relatively large amount of biliary excretion in rats. The rapid excretion of coumarin metabolites in the urine of human subjects given coumarin suggested that there is little or no biliary excretion of coumarin metabolites in humans.
The large difference in metabolism and elimination of coumarin between rats and humans suggested that the rat is not an appropriate animal model for the evaluation of the safety of coumarin for humans (Lake, 1999) (Loew and Koch, 2008).

Pharmacokinetic interactions

Due to the coumarin content of the roots of *P. sidoides* an enhancement of the anticoagulant action of coumarin derivative preparations by co-administration of Pelargonium root extract is theoretically possible. Koch and Biber (Koch and Biber, 2007) investigated whether a change in blood coagulation parameters or an interaction with coumarin-type anticoagulants occurred after administration of EPs® 7630 to rats. No effect on (partial) thromboplastin time (PTPT/TPT) or thrombin time (TT) was observed after oral administration of EPs® 7630 (10, 75, 500 mg/kg) for 2 weeks, while treatment with

warfarin (0.05 mg/kg) for the same period resulted in significant changes in blood coagulation parameters. If EPs® 7630 (500 mg/kg) and warfarin (0.05 mg/kg) were given concomitantly, the anticoagulant action of warfarin was not influenced. Similarly, the pharmacokinetics of warfarin was unchanged after pretreatment with EPs® 7630 for 2 weeks.

Moreover, the coumarins so far identified in EPs® 7630 do not possess the structural characteristics needed for anticoagulant activity. The minimal structural requirements for anticoagulant activity in coumarins are an hydroxyl group in position 4 and a non-polar rest in position 3 (Figure 3).



warfarin

Figure 3. Minimal structural requirements for anticoagulant characteristic in coumarins

In view of these results, it does not appear very probable that an increased bleeding tendency can arise in patients treated with EPs® 7630 (Loew and Koch, 2008) (Brendler and Wyk, 2008).

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

Toxicological data regarding Pelargonium preparation

In a cytotoxicity study with a preparation containing the tincture 1:10 (ethanol 9-11% m/m) of *Pelargonium sidoides* roots did not produce significant cytotoxic effects on human blood cells and human liver cells in the cell viability test and membrane integrity test within the concentration range tested (30, 100, 300 and 1000 µg/ml). In the human liver cells (HepG2 cells) the extracts produced a slight reduction in cell viability of approximately 20% only at the highest test concentration. Similarly, the extract samples did not produce any cytotoxic effects in the membrane integrity test in both THP-1and HepG2 cells (Jäggi et al., 2005).

In the brine shrimp lethality bioassay, neither Pelargonium extracts nor its phenolic constituents including benzoic and cinamic acid derivatives, hydrolysable tannins and C-glycosylflavones showed any cytotoxic effects. With LC_{50} values of > 1000 µg/ml and > 200 µg/ml for extracts and test compounds, respectively, it was concluded that the cytotoxic potential of ethanolic-aqueous root extract of *Pelargonium sidoides* and constituents may be negligible, when compared with the LC_{50} of the reference compounds actinomycin and podophyllotoxin (0.53 µg/ml and 72 µg/ml, respectively) (Kolodziej, 2002).

Conrad et al. (2007c) performed toxicological studies of EPs® 7630: cytotoxicity, acute and 4- week toxicology in rats, 2-week dose verification and 13-week toxicology in dogs, Ames test, chromosome-aberration test, micronucleus test in mouse cells, tumour promotion, local tolerability, immunotoxicity and reproduction toxicology. All the tests showed no negative effects. The full details of the toxicological investigation were not given.

In subacute and chronic toxicological studies in rats and dogs revealed a NOEL > 750 mg/kg body weight of EPs® 7630. Applying the recommended dose, the daily intake of 60 mg of extract would be equivalent to 4 and 1 mg/kg body weight (15 kg for a child or 60 kg for an adult, respectively) translating into a safety factor of more than 100 (Loew and Koch, 2008).

Toxicological data regarding constituents of Pelargonium extract

A number of animal studies have examined the mutagenic and carcinogenic potential of coumarin. Overall, the data suggest that coumarin is not a genotoxic agent. However, high doses of coumarin produced liver and lung tumors in some chronic studies. The 3,4-epoxidation pathway of metabolism to yield toxic metabolites explain this phenomenon, not the direct cytotoxic effect (Lake, 1999).

Rajalakshmi et al. (2001) established the safety of gallic acid in mice. In the study, acute administration of gallic acid even at a dose as high as 5 g/kg body weight did not produce any signs of toxicity or mortality. In the subacute 28-day study, gallic acid at a dose of 1000 mg/kg body weight did not significantly alter the haematological parameters. Further, no appreciable change was noted in the various biochemical parameters such as Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT), as well as many serum constituents such as plasma protein, cholesterol, urea and bilirubin. The organ weight of the treated animals did not vary significantly from the control, except for a decrease in the spleen weight. Histological examination of the tissues showed no marked treatment-related changes with respect to any of the organs examined, including spleen.

Subchronic toxicity of gallic acid (GA) was investigated in rats by feeding a diet containing 0-5% GA for 13 weeks. Toxicological parameters included clinical signs, body weight, food consumption, hematology, blood biochemistry, organ weights and histopathological assessment were observed. The results of hematological examinations suggested development of anemia, of probably hemolytic origin. However, the severity of the anemia was weak even at 5% gallic acid in diet. The NOAEL was estimated to be 119 mg/kg and 128 mg/kg for male and female rats, respectively (Niho et al., 2001).

Hepatotoxicity

Some investigations have examined the hepatic biochemical and morphological changes produced in the rats by coumarin administration from 1 week to 2 years. The coumarin-induced hepatotoxicity in the rodents can be attributed to the excretion of coumarin metabolites in the bile, thus the enterohepatic circulation enhance the exposure of liver cells to toxic coumarin metabolites, such as o-HPA and o-HPAA (see upper). The different metabolism and excretion in humans can explain the low risk of coumarin-induced hepatotoxicity in humans (Lake, 1999).

Koch (2006) examined the hepatotoxic effect of extracts from the roots of *Pelargonium sidoides*. Consequently, the studies on rats and dogs involving the oral administration of up to 3000 mg/kg EPs® 7630 p. o. provided no evidence of liver damaging effects. There were no effect on plasma transaminase, lactate-dehydrogenase and alkaline phosphatase activities and the level of bilirubin. These positive results were backed up by *in vitro* tests on human hepatocytes and hepatoma cells. The effect on cell viability did not observed after pretreatment with EPs® 7630 (0-50 µg/mL) for 24 hours.

The hepatotoxic risk is present only in specific compounds related to the overall group of coumarins. These substances are structurally different from the 7-hydroxy-coumarins contained in EPs® 7630 which, according to scientific literature, do not have hepatotoxic properties.

3.4. Overall conclusions on non-clinical data

The pharmacological results provide a rationale for the therapeutic application of *Pelargonium* extract. The moderate antibacterial effect against several Gram positive and Gram negative bacteria, interfering with invasion and adherence of microorganisms to human cells, triggering immune responses and mucolytic properties (via improving ciliar function) a complex mechanism of action of *Pelargonium sidoides* preparations. The identity of the pharmacologically active constituents is partly known.

Although there is limited knowledge about pharmacokinetic parameters and toxicological data of *Pelargonium* extract, the current non-clinical results (including data regarding the constituents) suggest that the application of *Pelargonium* preparation is probably safe.

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 relevant data available.

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

No relevant data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

A dose-finding, randomized, placebo controlled, double-blind study was carried out to compare three different doses of EPs® 7630 versus placebo in tablet preparations (10, 20, 30 mg, three times daily). 405 patients suffering from acute bronchitis were included in the study. The outcome measures were changes in bronchitis symptoms score (BSS) at day 7 and changes in individual components of BSS (Table 3). The decrease of BSS score was significantly higher in patients treated with any doses of EPs® 7630 compared to patients treated with placebo, but there was no significant difference between BSS of patients treated with different doses of EPs® 7630 (Schulz, 2008a).

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
Schulz, 2008a	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 405 mean age: 40 30% male	101/101/101 patients EPs® 7630 10/20/30 mg, 3 times daily 102 patients placebo duration: 7 days	1st reduction of BSS on day 7 2nd AEs	4.3/6.1/6.3 points for the 30/60/90 mg/d doses, respectively vs. 2.7 points 22/101, 25/101, 31/101 for the 30/60/90 mg/d doses, respectively vs. 14/102

Table 3. Dose-finding studies with EPs® 7630

Abbreviations: DB=double-blind, PC=placebo-controlled, R=randomized

4.2.2. Clinical studies (case studies and clinical trials)

Acute bronchitis

Matthys et al. (2003), Chuchalin et al. (2005), Matthys and Heger (2007a) and Matthys and Funk (2008) carried out randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of EPs® 7630 (30 drops three times daily) compared to placebo, in patients with acute bronchitis. The trials were performed according to a similar design. Patients, who met the following criteria, were suitable for the trial: age >18 years, acute bronchitis, duration of complaints (≤48 hours) and Bronchitis Severity Score (BSS) ≥5 points. The main exclusion criteria were an indication for antibiotic treatment or treatment with antibiotics during the period of 4-weeks prior to enrolment in the trial, allergic bronchial asthma, tendency to bleed, severe heart, renal or liver disease, immunosuppression, known or supposed hypersensitivity to trial medication. Following enrolment (day 0), control examinations occurred on day 3-5 and day 7.

The primary outcome criterion was the change of BSS on day 7. BSS scores comprise the most important features of acute bronchitis, namely, cough, sputum, rales/rhonchi, chest pain during coughing and dyspnea. Each symptom was assessed by the investigator using a verbal five-point rating scale ranging from zero to four. The secondary outcome criteria were variable; the main ones were disappearance or improvement of individual symptoms (fever, fatigue, pain in limbs, headache and hoarseness), duration of illness, days-off work and satisfaction with treatment. Some studies measured patients' health status using health-related quality of life questionnaires. Safety outcome criteria were the number, type and severity of adverse events (AEs) and tolerability, based on a verbal and laboratory tests.

The main results are summarized in Table 4. In each study the decrease of BSS was significantly higher in patients treated with EPs® 7630 compared to patients treated with placebo (Figure 4). The meta-analysis of these treatments also showed a significant decrease of BSS score compared to placebo (Agbabiaka et al., 2008). All individual symptoms recovery and/or improvement rates were higher in the EPs® 7630-treated group compared to placebo group. Remission by day 4 occurred in 69% of the patients under active substance treatment, compared to 33% of patients under placebo (Chuchalin et al, 2005). Treatment with EPs® 7630 shortened the duration of working inability for nearly 2 days. Complete recovery by day 7 was observed by the physician in 45.4% of patients taking active treatment compared to 6.4% of patients on placebo (Matthys and Heger, 2007a). Health-related quality of life improved more in patients treated with EPs® 7630 compared to placebo-treated patients. EPs® 7630 was well-tolerated, mild to moderate AEs were observed in all trials, but there were no significant differences in the number of AEs reported between two treatment groups (Matthys and Heger, 2007a). Some of AEs reported included gastrointestinal disorders, nervous system disorders (nervousness, fatigue, headache and restlessness), ear and labyrinth disorders (Matthys et al., 2003).

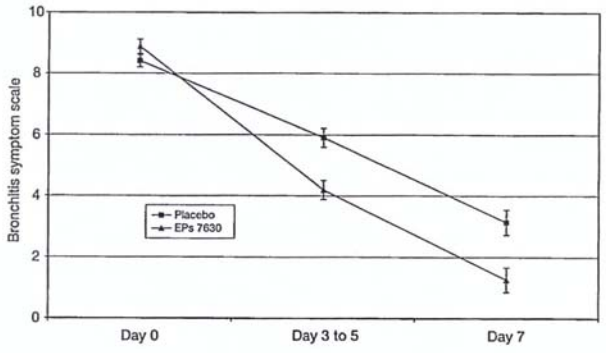


Figure 4. Bronchitis-symptoms score (BSS) at different visits for two treatment groups (mean ± 95% confidence interval) (Matthys and Heger, 2007a)

Table 4. Placebo-controlled clinical studies with EPs® 7630 – treatment of acute bronchitis

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
Matthys et al., 2003#	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 468 mean age: 41.1 vs.39.9 40.3 vs. 46.9% male	233 patients EPs® 7630 30 drops, 3 times daily 235 patients placebo duration: 7 days	1st reduction of BSS on day 7 2nd disappearance or improvement of individual symptoms on day 7: cough chest pain during cough symptom sputum rales/rhonchi dyspnoe 2nd working inability on day 7 2nd satisfaction with treatment (patients) 2nd adverse events ear and labyrinth gastrointestinal	5.9±2.9 points vs. 3.2±4.1 points (p<0.0001) 89.2% vs. 56.6% (p<0.0001) 83.7% vs. 48.1% (p<0.0001) 66.0% vs. 47.7% (p<0.0002) 77.1% vs. 44.4% (p<0.0001) 84.1% vs. 46.7% (p<0.0001) 15.9% vs. 43.0% (p<0.0001) 74.7% vs. 42.1% 8.6% vs. 6.8% 2.2% vs. 0.4% 1.7% vs. 3.0%
Chuchalin et al., 2005*	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 124 mean age: 36.2 vs.35.9 23.4 vs. 36.7% male	64 patients EPs® 7630 30 drops, 3 times daily 60 patients placebo duration: 7 days	1st reduction of BSS on day 7 2nd BSS<5 points on day 7 2nd disappearance of individual symptoms on day 7: rales/rhonchi chest pain during cough cough 2nd completely recovery rates on day 7 2nd satisfaction with treatment (patients) 2nd adverse events	7.2±3.1 points vs. 4.9±2.7 points (p<0.0001) 95.3% vs. 58.3 % (p<0.001) 91.7% vs. 49.2% (p<0.0001) 94.8% vs. 55.8% (p<0.0001) 31.3% vs. 5.0% (p<0.0001) 84.4% vs. 30.0% 79.7% vs. 43.3% 23.4% vs.16.7%
Matthys and Heger, 2007a*	DB,PC,R, MC	acute bronchitis present (≤48 hours) BSS ≥5 points n= 217 mean age: 37.4 24.4% male	108 patients EPs® 7630 30 drops, 3 times daily 109 patients placebo duration: 7 days	1st reduction of BSS on day 7 2nd complete remission of individual symptoms on day 7: cough chest pain during cough symptom sputum rales/rhonchi dyspnoe 2nd complete recovery 2nd satisfaction with treatment (patients) 2nd adverse events	7.6±2.2 points vs. 5.3±3.2 points (p<0.0001) 51.9% vs. 11.9% 93.4% vs. 86.0% 68.3% vs. 40.0% 88.2% vs. 50.0% 87.9% vs. 76.7% 45.4% vs. 6.4% 84.3% vs. 47.7% 21.3% vs. 22.0%
Matthys and Funk, 2008	DB,PC,R, MC	acute bronchitis present (≤48 hours) BSS ≥5 points n= 217 mean age: 37.4 24.4% male	108 patients EPs® 7630 30 drops, 3 times daily 109 patients placebo duration: 7 days	1st reduction of BSS on day 7 2nd treatment response (BSS< 3 points on day 7) 2nd complete remission of individual symptoms on day 7: cough chest pain during cough symptom sputum rales/rhonchi dyspnoe 2nd working inability on day 7 2nd satisfaction with treatment (patients) 2nd adverse events	7.6±2.2 points vs. 5.3±3.2 points (p<0.0001) 74.1% vs. 26.6% 51.9% vs. 11.9% 93.4% vs. 86.0% 68.3% vs. 40.0% 88.2% vs. 50.0% 87.9% vs. 76.7% 18.4% vs. 33.3% 84.3% vs. 47.7% 21.3% vs. 22.0%

Abbreviations: DB=double-blind, PC=placebo-controlled, R=randomized, MC= multicentre, * studies included in Cochrane Meta-analysis # studies excluded in Cochrane Database (Timmer et al., 2009)

Matthys et al. (2007) designed a multicentre, prospective, open observational study. A total of 2099 patients aged 0-93 years old with productive cough for less than six days without indication for treatment with antibiotics were given EPs® 7630 in age-dependent dosage (the results of treatment of children, see section 4.2.3.). Adults and children > 12 years (n=1731) were instructed to take 30 drops of EPs® 7630 three times daily over a period of 14 days. At baseline the mean value of BSS of all patients was 7.1±2.9 points. At the third follow-up the mean value was 1.0±1.9 points (Figure 5, Table 5). According to the response criterion that was defined as the decrease of BSS with at least five points from baseline to the third follow-up, the responder rate was 68.0%. The remission rate at the last observation for five bronchitis-specific symptoms was above 80% each, except for cough, which showed a remission rate of 59.7% (Figure 5). The investigators documented complete recovery for 1458/2099 patients at the last visit. A total of 28 adverse events occurred, but none of them was serious or significant. 11/28 AEs were classified as "gastrointestinal disorders".

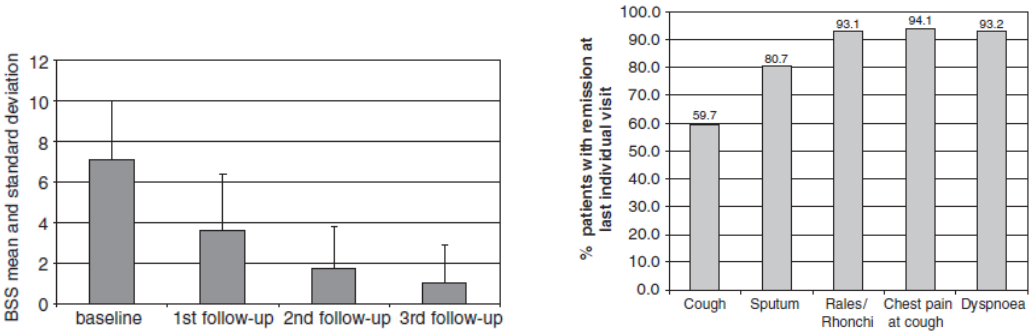


Figure 5. BSS changes during the study period in all patients and remission rates from baseline to last observation for bronchitis-specific symptoms in all patients (Matthys et al., 2007)

The efficacy of EPs® 7630 was investigated in a prospective, open, multicentre study with 205 patients suffering from acute bronchitis (87.8%) or acute exacerbation of chronic bronchitis. The main outcome measure was the change in the total score of five symptoms (cough, expectoration, wheezing, chest pain during coughing and dyspnoea) typical for bronchitis, which were each rated using a 5-point scale. The mean total score of these symptoms was 6.1±2.8 points at baseline; at the final examination on day 7 this was 2.8±2.6 points (Table 5.). The remission rate of individual symptoms was over 70%. Seventy eight per cent of the patients were satisfied with the treatment at the final visit. Eighteen adverse events were documented; eleven cases were AEs involving the gastrointestinal tract. A serious adverse event was not reported. The disadvantage of this study is that 48.8% of the patients reported the use of other therapy measures (inhalation of chamomile or saline solution, antitussive, mucolytic agent, nasal douches) in addition to taking EPs® 7630 (Matthys and Heger, 2007b).

Table 5. Open clinical studies with EPs® 7630 – treatment of acute bronchitis

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
Matthys et al., 2007	MC, P, OO	productive cough for less than 6 days n= 2099 mean age: 34.5 41,0% male	all adult patients: EPs® 7630 30 drops, 3 times daily duration: 14 days	1st decrease of BSS of at least five points 2nd remission rate of bronchitis specific symptoms 2nd remission rate of other symptoms 2nd complete recovery at last visit 2nd AEs	responder rate 68.0% ~80% ~80% 1458/2099 26/2099 (1.2%)
Matthys and Heger, 2007b#	MC, P, OO	acute bronchitis (87.8%) or acute exacerbation of chronic bronchitis present (≤ 7 days) n= 205 mean age: 42 33.2% male	all patients: EPs® 7630 30 drops, 3 times daily duration: 7days	1st decrease of mean score of bronchitis typical symptoms 2nd remission rate of bronchitis specific symptoms 2nd remission rate of other symptoms 2nd satisfaction with the treatment 2nd AEs	3.3±3.8 points >70% 66.9-88.2% 78% 18/205

Abbreviations: MC= multicentre, P=prospective, OO=open observational, # studies excluded in Cochrane Meta-analysis (Timmer et al., 2009)

Acute sinusitis

A multicentre, prospective, open study investigated the efficacy and change in symptoms in 361 patients (aged 1-94 years) with acute sinusitis and acute exacerbation of chronic sinusitis under administration of EPs® 7630. Adult patients suffering from acute sinusitis received 30 drops every hour up to 12 times on day 1 and 2 and 3 x 30 drops daily on day 3-28. Children under 12 years of age were suggested to take 20 drops every hour up to 12 times on day 1 and 2 and 3 x 20 drops daily on day 3-28. Patients with exacerbation of chronic sinusitis received prophylactic therapy: 2 x 30 drops for adults or 2 x 20 drops for children for another 8 weeks (long term treatment). Following the entrance examination, patients were examined after 7, 14 and 28 days; patients under the long term treatment on day 56 and day 84. A total of 33.5% of patients used co-medication, such as expectorants and antitussive remedies. The primary outcome criteria was the sum of objective and subjective symptoms of the sinusitis score from day 0 to the end of the treatment according to a five-point verbal rating scale. The mean total score of symptoms was 15.2±4.6 points at baseline; at the final examination on day 28 this was 2.4±3.2 points (Table 6.). On the last day of treatment within 4 weeks 80.9% of the patients became symptom-free or experienced a clear improvement in their symptoms. A total of 56/361 patients (15.5%) reported adverse events (mostly gastrointestinal complaints) during the trial. In 17 cases, the causal relationship with the study medication could not be ruled out (Schapowal and Heger, 2007).

Bachert et al. (2009) investigated the efficacy and safety of EPs® in case of rhinosinusitis in a multicentre, randomized, double-blind, placebo-controlled trial. Patients with an age ranging from 18 to 60 years with radiographically confirmed acute rhinosinusitis and a Sinusitis Severity Score (SSS) of 12 points or greater were eligible. The SSS was calculated as the sum of the 6 symptoms scores (headache, maxillary pain, maxillary pain worsening on bending forward percussion or pressure, nasal obstruction, purulent nasal secretion, purulent nasal discharge visualized in the middle meatus or purulent postnasal discharge) as assessed on a 5 point verbal rating scale ranging from 0-4. Patients were instructed to take 60 drops EPs® 7630 three times daily. Study medication was taken for maximal period of 22 days.

The primary outcome measure was defined as the change of Sinus Severity Score at day 7 of treatment compared to baseline. The main secondary outcome criteria were responses defined as an SSS< 10 points on day 7, a reduction of at least 4 points on day 7, occurrence of complete remission (SSS=0 on day 21) and treatment outcome assessed by the patients and the investigators. The mean decrease in the primary outcome was 5.5 points in the EPs® 7630 and 2.5 points in the placebo group, resulting in a between group difference of 3.3 points ($p<0.00001$). This result was confirmed by all secondary parameters indicating a more favorable course of disease and a faster recovery in the EPs® 7630 group. A total of 8/103 patients reported at least one adverse event during the trial, 6/51 in the EPs® 7630 group and 2/52 in the placebo group. All adverse events were assessed as non-serious. In four cases (gastrointestinal complaints-3x, allergic skin reaction-1x) that occurred in the EPs® 7630 group, the causal relationship with the study drug could not be excluded.

Common cold

Lizogub et al. (2007) evaluated the efficacy and tolerability of EPs® 7630 compared to placebo in adult patients with common cold. One hundred and three patients with at least two major (nasal discharge, sore throat) and one minor (nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches and fever) or with one major and three minor cold symptoms present for 24 to 48 hours were randomized to receive either 30 drops of EPs® 7630 or placebo three times daily. The study had a high-dose arm (3 x 60 drops of EPs® 7630 compared to placebo), but the results of high-dose treatment were not reported in the manuscript. The main exclusion criteria were the presence of any other ear, nose, throat and respiratory disease than common cold, positive rapid test for group A beta-hemolytic streptococcus and treatment with other medicines (e.g. antibiotics, decongestants, cough relief medications) that might impair the trial results.

The primary outcome criteria was the sum of symptom intensity differences (SSID) of the cold intensity score (CIS) from day one to five according to a five-point verbal rating scale. The main secondary outcome criteria were changes of individual symptoms of the CIS, changes of further cold-relevant symptoms, ability to work and satisfaction with treatment. From baseline to day five, the mean SSID improved by 14.6 points in EPs® 7630 treated group compared with 7.6 points in the placebo group ($p<0.0001$) (Table 6.). After 10 days, 63.5% versus 11.8% in the EPs® 7630 versus placebo group were clinically cured (CIS=0). The main duration of inability to work was significantly lower in the EPs® 7630 treated patients (6.9 days) than in the placebo group (8.2 days). The treatment outcome was assessed as better in the EPs® 7630 group than in the placebo group by both the investigator and the patients on day five.

Three of 103 patients experienced adverse events: two of 52 patients (3.8%) in the EPs® 7630 and one of 51 patients (2.0%) in the placebo group. None of these events were classified as serious. A causal relationship to the study drug could not be excluded in one treated patient (mild epistaxis).

Table 6. Clinical studies with EPs® 7630 – treatment of acute sinusitis and common cold

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
Schapowal and Heger, 2007	MC, O	acute sinusitis or acute exacerbation of chronic sinusitis n= 361 (1-94 years) mean age: 38±19	EPs® 7630 adults: 30 drops every hours up to 12 times on day 1 and 2; 3x30 drops daily from day 3 Children (<12 years): 20 drops every hours up to 12 times on day 1 and 2; 3x20 drops daily from day 3 duration: Acute sinusitis: 28 days Exacerbation: 28 days+ 8 weeks prophylaxis – (2x 30 drops daily for adults and 2x20 drops daily for children)	1st reduction of total score of objective and subjective symptoms 2nd complete remission or improvement of individual symptoms on day 28 2nd AEs	day 0: 15.2±4.6 day 28: 2.4±3.2 80.9% 56/361 (15.5%)
Bachert et al., 2009*	DB,PC,R, MC	acute rhinosinusitis present at least 7 days SSS ≥12 points n= 103 mean age: 34.4 vs. 35.6 37% vs. 33% male	51 patients EPs® 7630 60 drops, 3 times daily 52 patients placebo duration: maximum 22 days	1st reduction of SSS at day 7 2nd SSS< 10 points on day 7 2nd complete remission (SSS=0 on day 21) 2nd AEs	5.5 points vs 2.5 points (p<0.00001) 67% vs. 27% (p<0.0001) 61% vs. 10% (p<0.001) 11.8 % vs. 3.8%
Lizogub et al., 2007*	DB,PC,R, MC	common cold present 24-48 hours max. symptoms score 40 n= 103 mean age: 34.5 vs. 37.4 30.7% vs. 31.3% male	52 patients EPs® 7630 30 drops, 3 times daily 51 patients placebo duration: maximum 10 days	1st reduction of SSID at day 5 2nd patients with clinically cure on day 10 2nd duration of inability to work (days) 2nd AEs	14.6±5.3 points vs 7.6±7.5 points (p<0.0001) 63.5% vs. 11.8% (p<0.0001) 6.9±1.8 vs. 8.2±2.1 (p<0.0003) 3.8% vs. 2.0%

Abbreviations: DB=double-blind, PC=placebo-controlled, R=randomized, MC= multicentre, O=open,

* studies included in Cochrane Database

studies excluded in Cochrane Meta-Analysis (Timmer et al., 2009)

A review article presented a multicentre post-marketing surveillance study, which was carried out in 641 patients with respiratory tract infections e.g. tonsillitis, rhinopharyngitis, sinusitis and bronchitis. Outcome criteria were the change in the subjective and objective symptoms during the treatment of EPs® 7630 and an assessment of treatment outcome by both physicians and patients on a 4-point rating scale. After 2 weeks of therapy, a total of 85% of the patients showed complete recovery or major improvement. No adverse reaction was observed (Kolodziej, 2002).

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

Dose-finding study

Kamin et al. (2010a) carried out a double-blind, placebo-controlled dose-finding study for EPs® 7630 performed in children and adolescents. A total of 399 patients (aged 6–18 years) were randomized to receive either 30 mg, 60 mg or 90 mg EPs® 7630 film-coated tablets or placebo daily. Patients suffering from acute bronchitis with symptoms starting <48 h prior to inclusion in the study and with a total score of bronchitis-specific symptoms (BSS) >5 points at screening were included in the study. Individual duration of the study was 7 days. During this time, 3 visits were scheduled (day 0; days 3–5; day 7). The primary efficacy endpoint was the change in the BSS total score from day 0 to day 7

rated by the investigator. The main secondary outcome measurements were treatment response according to three criteria, change of individual symptoms of total score, change of general symptoms and satisfaction with the treatment.

The decrease in the BSS total score between day 0 and day 7 was more pronounced in the active treatment groups compared with that in the placebo group (Table 7). The subsequent pairwise comparisons of each active treatment group with placebo using the ANCOVA model revealed statistically significant differences in the decrease in the BSS total score for the EPs® 7630 60 mg and 90 mg groups ($p = 0.0004$ and $p < 0.0001$, respectively).

The treatment response calculated on the basis of the BSS total scores was higher in the active treatment groups than in the placebo group (Figure 6). Statistically, significant differences regarding criterion 1 were determined for the 60 mg and 90 mg EPs® 7630 groups in comparison with placebo. Regarding criteria 2 and 3, a significant difference in the rate of responders compared with placebo was observed for the 90 mg EPs® 7630 group. The mean decrease in the individual symptoms from day 0 to day 7 was markedly more pronounced in the EPs® 7630 (60 mg) and EPs® 7630 (90 mg) groups than in the placebo group. Pairwise comparisons with placebo showed statistically significant advantages of EPs® 7630 in the 60 mg and 90 mg group for the symptoms.

A total of 80 adverse events were observed in 77 of 400 patients (19.3%). The most frequent adverse events were gastrointestinal disorders (11%). With 22.8% (in EPs® 7630 30 mg group), 17.2% (in EPs 7630 60 mg group) and 19.2% (in EPs® 7630 90 mg group) respectively, the frequency of adverse events in the active treatment groups was similar to that in the placebo group (17.8%). None of the adverse events was classified as serious.

The authors concluded that based on the efficacy and safety results, a daily dose of 60 mg EPs® 7630 could represent the optimal dose with respect to the benefit/risk ratio.

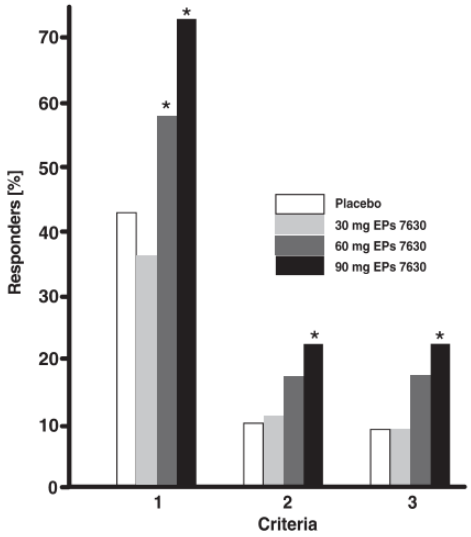


Figure 6. Treatment response. Frequency of responders for 3 criteria:

criterion 1: BSS total score < 3 points at day 7;
criterion 2: decrease in BSS total score of at least 7 points from day 0 to day 7;
criterion 3: combination of criteria 1 and 2.

Clinical studies

- Acute bronchitis

Blochin et al. (1999) examined the efficacy and tolerability of Pelargonium extract in comparison to acetylcystein for children with acute bronchitis in a multicentre, randomized, controlled open trial. Sixty children aged between 6-12 years were randomized into two groups to receive either Pelargonium extract (20 drops every hours up to 12 times on day 1 and 2; 20 drops daily on day 3-7) or acetylcystein granules (2 x 200 mg daily for 7 days). 100 g of Pelargonium solution contained 80 g of ethanolic extract (1+10) from the roots of *P. sidoides/reniforme.*

The overall scores of bronchitic symptoms of participations were not less than 5 points and onset of complaints was within the last 48 hours. The main exclusion criteria were compulsory indication for antibiotic therapy, asthma bronchiale, heart, kidney, liver diseases, immunosuppression and hypersensitivity to study medication.
Outcome measures were changes in typical symptoms of bronchitis. These symptoms were assessed on the basis of a 5-rating scale. General symptoms, questions around the general state of health and therapeutic tolerability were also evaluated. After 7 days, the overall score of bronchitic symptoms decreased by 7±2 points in the Pelargonium group and 6±3 in acetylcystein group (p=0.285). There were no statistically significant differences between the two groups in relation to reduction of bronchitis-specific symptoms. The full remission of all bronchitic symptoms was 76.7% in the Pelargonium group and 56.7% in the acetylcystein group (p=0.17) (Table 7). Adverse events were not found. Both the trial physicians and the patients rated the tolerability as very good or good in all cases.

Haidvogl and Heger (2007) described an open, uncontrolled study which 742 children (aged between 0-12 years) with acute bronchitis or acute exacerbation of chronic bronchitis were treated with EPs® 7630 (children up to 2 years: 3 x 5 drops, 2-6 years: 3 x 10 drops, over 6 years: 3 x 20 drops), for a mean period of 14 days. The exclusion criteria included antibiotic treatment in the pre-phase, liver disease and blood coagulation disorders. Five bronchitic specific symptoms (BSS) were summed up to give an overall measure of disease severity. Non-specific disease symptoms (loss of appetite, headache, vomiting and fever) were also recorded, together with adverse events. Concomitant medication for a part of patients (48.2%) was antitussive and broncholytic agents. The overall BSS score decreased during the treatment from 6.0±3.0 points at baseline to 2.7±2.5 points after 1 week and to 1.4±2.1 points at the end of the study. According to overall BSS score, complete or partial remission of bronchitis was achieved in 90.2% of children. The non-specific symptoms also improved substantially. During the course of study, 13 adverse events were documented. In 8 cases, a causal relationship to the test medication was not excluded (exanthema, psychomotor unrest with crying fits, dyspnoe and diarrhoea). In a total of 5 of these patients, the test medication was discontinued.

Matthys et al., (2007) examined the efficacy and safety of treatment with EPs® 7630 in patient (aged 0-93 years) with acute bronchitis in an open observational trial. Four hundred and twenty patients were between 3-18 years of age and 78 patients were under 3 years of age. The dosage of EPs® 7630 was adapted to age as follows: >12 years: 3 x 30 drops daily, 6-12 years: 3 x 20 drops/day and <6 years: 3 x 10 drops. In the subgroup of children, the decrease of BSS was 3.3±2.6 points, 1.6±1.9 points and 0.9±1.8 points at the first, second and third follow-up, respectively (Figure 7).

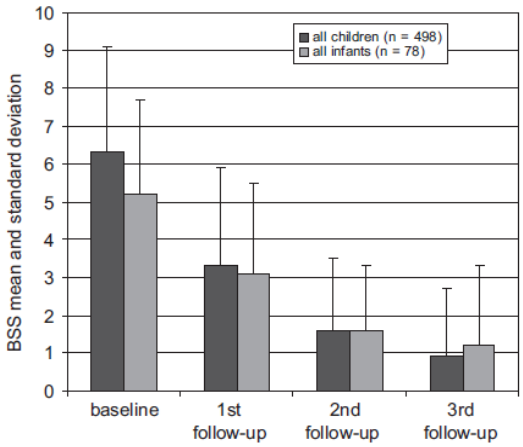


Figure 7. BSS changes during the study period in children and infants.

(Matthys et al., 2007)

13/420 adverse events occurred in children and 3/78 in infants. Severe adverse events were documented in the subgroup of children and were coded in the organ class "infections and infestations", but none was assessed as related to study medication. In one child the relation to medication of a hypersensitivity reaction was assessed as possible.

A randomized, double-blind, placebo-controlled study was carried out to evaluate the efficacy of EPs® 7630 compared to placebo in children (1 to 18 years old) with acute bronchitis. Patients (study 1: n=220, study 2 n=200), who met the following criteria, were suitable for the trial: acute bronchitis, duration of complaints (≤48 hours) and Bronchitis Severity Score (BSS) ≥5 points. Children between 1-6 years were given 3 x 10 drops/day, children between 6-12 years were given 3 x 20 drops daily and children over 12 years were given 3 x 30 drops/day. The primary efficacy parameter was the change in the total score of the five bronchitis specific symptoms (BSS) – assessed by the physicians by the use of a five point verbal rating test. The mean decrease of BSS was 3.4 (study 1), 4.4 (study 2) points in the EPs® 7630 and 1.2 (study 1), 2.9 (study 2) points in the placebo group, resulting in a significant difference between treatment and placebo group ($p<0.0001$). Adverse events were observed in 31/103 in the EPs® 7630 group and 24/97 in the placebo group (study 1). A causal relationship to the study drug could not be excluded in six treated patients (5: gastrointestinal problems and 1: allergic skin reaction). In case of study 2, a total of 2/220 patients reported adverse events during the trial (Schulz, 2008b).

Kamin et al. (2010b) demonstrated the efficacy of EPs® 7630 in the treatment of patients (1-18 years) with acute bronchitis outside the strict indication for antibiotics. A total of 200 patients were randomized to receive either EPs® 7630 (1-6 years: 3 x 10 drops, 6-12 years: 3 x 20 drops, 12-18 years: 3 x 30 drops, daily) or placebo for 7 consecutive days. Primary outcome measure was the change in the total score of BSS from day 0 to day 7. Main secondary outcome criteria were treatment outcome, satisfaction with treatment and bed rest.

From baseline to day 7, the mean BSS score improved significantly more for EPs® 7630 compared to placebo (3.4±1.8 vs. 1.2±1.8 points, $p<0.0001$). On day 7, treatment outcome was significantly better, satisfaction with treatment was more pronounced and time of bed rest was shorter as compared to placebo.

Kolodziej (2002) presented three clinical trials, which investigated the efficacy of treatment with Pelargonium extract in children suffering from acute bronchitis, angina catarrhalis and acute tonsillitis. One thousand and forty two children with acute bronchitis (up to 12 years) were treated with

Pelargonium extract. This prospective, multicentre observational study concluded that the remission or improvement rate of all individual symptoms (cough, expectoration, difficulty in breathing, wheezing and chest pain) was over 80%.

In a prospective, randomized, controlled trial involving 60 children between 6 and 10 years with angina catarrhalis, the response rate after 4 days of treatment with Pelargonium extract was 76% compared to that of 30% with symptomatic treatment.

In randomized, double-blind, placebo-controlled trial, 78 children with acute tonsillitis were treated with Pelargonium extract or placebo for 6 days. The primary outcome criterion was the response rate defined as total score of tonsillitis specific symptoms <4 points at day 4. The response rates were 90.0% in the treated group and 44.7% in the placebo group ($p< 0.0001$). The mean decrease of total score was 6.8±2.8 points in the Pelargonium group and 3.7±3.3 points in the placebo group ($p< 0.0001$). Tolerability was rated as good or very good by 97.5% of patients treated with Pelargonium extract.

Haidvogl and Heger (2007) referred an uncontrolled observational study carried out by Dome and Schuster. The efficacy of treatment of acute bronchitis in 259 children with Pelargonium preparation was examined. The BSS decreased from 6.0±2.9 points to 2.3±2.8 points within 2 weeks. Only a few mild- and short-termed adverse events were recorded.

- Tonsillopharyngitis

In a multicentre, prospective, randomized, double-blind, placebo-controlled trial, the efficacy and safety of EPs® 7630 (3 x 20 drops daily) was examined and compared to placebo in 143 children aged 6-10 years suffering from acute non-streptococci-induced tonsillopharyngitis. The maximum duration of the complaints was 48 hours and the minimum degree of Tonsillopharyngitis Severity Score (TSS) was 8 points. The tonsillitis-specific symptoms (dysphagia, sore throat, salivation, rubour and fever) were rated using 4-point scale. Following the entrance examination patients were examined after 2, 4 and 6 days and the clinical findings recorded. Patients with a fever >38.5°C were allowed to be given paracetamol suppositories as additional medication. The most frequent premature withdrawal in EPs® 7630 group was lack of compliance (2/4), and the lack of efficacy in the placebo group (29/44).

The primary target criterion for assessing of the efficacy of EPs® 7630 was the decrease of TSS from baseline to day 4. The main secondary outcome criteria included change of individual symptoms and further complaints, treatment outcome according to the Integrative Medicine Outcome Scale. The decrease of the TSS to day 4 was 7.1±2.1 points under EPs® 7630 and 2.5±3.6 points under placebo ($p<0.001$) (Figure 8, Table 7). The remission rates of the individual symptoms dysphagia, fever and salivation on day 4 under EPs and placebo were at 60-79% and 47-27%, respectively, followed by sore throat with 32 and 16% and rubour with 6 and 1%. When assessing the therapeutic success, the trial physicians on day 4 observed freedom of complaints or a significant improvement in symptoms in 65/73 (89.0%) patients under EPs® 7630, as compared to the placebo group where 12/70 (17.1%) patients were free of complaints or showed significantly improved symptoms. Moreover, children in the EPs® 7630 group received paracetamol less frequently and over a significantly shorter time than children in the placebo group (1.6±0.9 g vs. 2.0±1.2 g paracetamol). The authors concluded that treatment with EPs® 7630 reduced not only the severity of symptoms, but also shortened the duration of illness by at least 2 days (bed rest on day 4: 15.1% vs. 62.9%).

Adverse events were observed in 1/73 in the EPs® 7630 group and 14/70 in the placebo group, but all events represented typical symptoms of the acute infection. None of the cases was correlated with the test medication (Heger and Bereznoy, 2002) (Bereznoy et al., 2003).

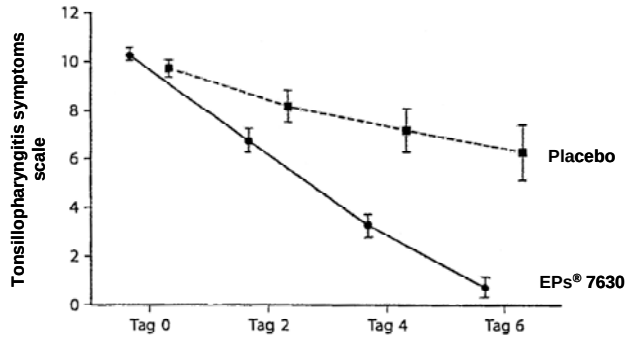


Figure 8. Decrease of the Tonsillopharyngitis Severity Score in the course of a 6-day therapy (Heger and Bereznoy, 2002) (Bereznoy et al., 2003)

Table 7. Clinical studies with *Pelargonium* extract– children

Study	Design	Study population	Treatment	Endpoints	Results (*Pelargonium* extract vs. placebo/comparator)
Kamin et al., 2010a	DB, PC, R **dose-finding study**	**ACUTE BRONCHITIS** present < 48 hours BSS ≥ 5 points n= 399 age: 6-18 years mean age: 12.7 51.9% male	EPs® 7630 – film-coated tablet 100 patient 3x10 mg 99 patient 3x20 mg 99 patient 3x30 mg placebo 101 patient duration: 7 days	1st reduction of BSS on day 7 2nd decrease of individual symptoms on day 7 2nd decrease of general symptoms on day 7 2nd AEs	EPs® 7630 (30 mg) - 3.6±2.4 p<0.0011 EPs® 7630 (60 mg) - 4.4±2.4 p<0.0001 EPs® 7630 (90 mg) - 5.0±1.9 p<0.0001 vs. placebo - 3.3±2.6 statistically significant dose-dependent effect EPs® 7630 (30 mg) – 22.8% EPs® 7630 (60 mg) – 17.2% EPs® 7630 (90 mg) – 19.2% vs. placebo – 17.8%
Blochin et al., 1999	MC, C, O	**ACUTE BRONCHITIS** present < 48 hours BSS ≥ 5 points n= 60 age: 6-12 years mean age: 8.5 vs. 8 33.3% vs. 63.3% male	30 patients *Pelargonium* extract 20 drops every hours up to 12 times on day 1 and 2; 20 drops daily on day 3-7 30 patients acetylcystein 2x200 mg daily for 7 days duration: 7 days	1st score of bronchitic symptoms at day 7 2nd elimination of individual symptoms on day 7: cough sputum	7±2 vs. 6±3 points (p=0.285) 76.7 vs. 56.7 83.3 vs. 71.4
Haidvogl and Heger, 2007	MC, O, UC	**ACUTE BRONCHITIS** acute exacerbation of chronic bronchitis (14.3%) n= 742 age: 0-12 years <2: 237 2-6: 321 >6: 168 mean age: 4±3 388/742 male	EPs® 7630 >2 years: 3x5 drops 2-6 years: 3x10 drops 6-12 years: 3x20 drops duration: 14 days	1st reducion of BSS on day 7 on day 14 2nd remission rate of individual symptoms cough sputum dyspnoe rales/rhonchi chest pain 2nd adverse events	 from 6.0±3.0 to 2.7±2.5 to 1.4±2.1 45.9% 68.7% 86.2% 73.2% 85.0% 13/742 (1.8%)

Matthys et al, 2007	MC, P, OO	**ACUTE BRONCHITIS** productive cough for less than 6 days n=498 >6-12: 127 <= 6: 241 years: 0-18	EPs® 7630 >6 years: 3x10 drops 6-12 years: 3x20 drops >12 years: 3x30 drops duration: 14 days	1st decrease of BSS 1st follow-up 2nd follow-up 3rd follow-up 2nd Adverse events	Baseline: 6.3±2.8 (<3 yrs: 5.2±2.5)) 3.3±2.6 points (3.1±2.4) 1.6±1.9 points (1.6±1.7) 0.9±1.8 points (1.2±2.1) 16/498
Schulz, 2008b	DB, PC, R	**ACUTE BRONCHITIS** present < 48 hours BSS ≥ 5 points n(1)= 220 n(2)=200 age: 1-18 years mean age: 9	Study 1: 103 patients EPs® 7630 1-6 years: 3x10 drops 6-12 years: 3x20 drops 12-18 years: 3x30 drops 97 patients placebo duration: 7 days	1st reduction of BSS on day 7 2nd adverse events	Study1: 3.4 vs. 1.2 points Study 2 4.4 vs. 2.9 points (p>0.0001) Study1: 30% vs. 25% Study 2: 2/220 (1%)
Kamin et al, 2010b	MC, R, DB, PC	**ACUTE BRONCHITIS** n= 200 age: 1-18 years	EPs® 7630 1-6 years: 3x10 drops 6-12 years: 3x20 drops 12-18 years: 3x30 drops placebo duration: 7 days	1st reduction of BSS on day 7 2nd satisfaction with treatment	3.4±1.8 vs. 1.2±1.8 points, p<0.0001 77.6% vs. 25.8%, p<0.0001
Heger and Bereznoy, 2002 Bereznoy et al., 2003	MC, R, DB, PC	non-streptococci-induced **TONSILLOPHARYNGITIS** present < 48 hours n= 143 age: 6-10 years mean age: 7.5 49% male	73 patients EPs® 7630 20 drops, 3 times daily 70 patients placebo duration: 6 days	1st change of TSS on day 4 2nd remission rate of tonsillitis specific symptoms dysphagia sore throat fever 2nd adverse events	7.1±2.1 vs. 2.5±3.6 points (p>0.001) 60.3% vs. 27.1% 31.5 vs. 15.7% 68.5 % vs. 33.3% 1.4% vs. 20%

Abbreviations: DB=double-blind, PC=placebo-controlled, R=randomized, MC= multicentre, O= open, C= controlled, UC= uncontrolled

4.3. Overall conclusions on clinical pharmacology and efficacy

This assessment report presents six clinical studies (including one dose-finding trial) (Schulz, 2008a) (Matthys et al., 2003) (Chuchalin et al., 2005) (Matthys and Heger, 2007a) (Matthys et al. 2007) (Matthys and Heger, 2007b), which examined the efficacy and safety of *Pelargonium sidoides* extract in adult patients with acute bronchitis. Children with acute bronchitis were treated with *Pelargonium* extract in six clinical trials (Kamin et al., 2010a) (Blochin et al., 1999) (Haidvogl and Heger, 2007) (Matthys et al, 2007) (Schulz, 2008b) (Kamin et al., 2010b). All clinical studies concluded the effectiveness of *Pelargonium* preparation in treating acute bronchitis. Overall seven studies were randomized, double-blind and placebo-controlled. Although the results of open studies are also promising, the lack of true control group, blinding and randomization limits the usefulness of these trials.

The majority of trials used uniform posology in adults, but there is heterogeneity in case of children regarding the dosage. Some trials offered to take 20 drops of liquid preparation every hour up to 12 times on first and second day of treatment, but no information was given on the true frequency of administration. Furthermore, the difference between the solution and tablets in bioavailability and phytochemical constituents is unknown. In case of some trials the concomitant medication prevents the objective evaluation of effectiveness of *Pelargonium* extract.

On the other hand, the definition of 'acute bronchitis' is still under discussion and the diagnosis is solely based on clinical findings without standardized diagnostic signs and sensitive or specific confirmatory laboratory tests. As a result of the current lack of standardized criteria, all outcomes applied in trials are subjective. The BSS score is not validated, but appears to be associated with a clinical benefit (Kamin et al., 2010). The Cochrane review on *Pelargonium sidoides* also drew attention that the studies used non-validated symptom scores as a primary outpoint and none of the trials were designed to examine time to complete symptom recovery based on a predefined clinically relevant difference. In spite of the shortcomings, the Cochrane review concluded that the herbal preparation may be effective in relieving symptoms in acute bronchitis in adults and children (Timmer et al., 2009). However, it was decided that because the non-validated BSS score was used in the trials, this indication can not be accepted at well-established use level.

The evaluation of the effects of the drug in adult patients with acute rhinosinusitis was based on two trials (Schapowal and Heger, 2007) (Bachert et al., 2009). These studies showed significant treatment effects for the alleviation of symptoms. Considering the small sample size and the lack of control in case of one study, these trials need to be repeated in order to allow a firm conclusion to be drawn on the use of *Pelargonium* extract in the treatment of acute sinusitis.

There was a single study on treatment of the common cold in adults (Lizogub et al., 2007). In the critical evaluation of this study, the reviewers concluded that *Pelargonium* preparation was effective in reducing symptoms associated with common cold, but the presentation of a high-dose arm of the trial would have given more confidence in the findings (Patrick and Hickner, 2008). The replication of these results may support the well-established use of *Pelargonium* extract in the treatment of common cold.

5. Clinical Safety/Pharmacovigilance

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

The safety of clinical trials was assessed with respect to the adverse events and the results of laboratory test. In placebo-controlled clinical studies there was no significant difference in the severity and frequency of adverse events between active treatment group and placebo group. However, the adverse events were almost always described as mild to moderate. Severe allergic reaction also occurred (see 5.3).

5.2. Patient exposure

The clinical trials referred in assessment report were conducted on over 3500 adult patients and approximately 3000 children suffering from acute bronchitis. Four hundred sixty four adults with acute sinusitis, 103 patients (>18 years) with common cold and 143 children with tonsillopharyngitis were exposed to *Pelargonium sidoides* treatment.

5.3. Adverse events and serious adverse events and deaths

There is a large number of studies and the section 4.2 and Table 3-7 contain a detailed presentation of adverse events observed during clinical trials. In these studies on the treatment of respiratory infections with an extract of *P. sidoides* the adverse events were assessed as being non-serious or minor or transitory. In a review article about the treatment of acute bronchitis with *Pelargonium* extract, the most frequent adverse events were light gastrointestinal complaints (diarrhoea, epigastric discomfort, nausea or vomiting, dysphagia). These gastrointestinal problems, which were usually harmless and disappeared spontaneously, could be associated with the tannins contained in *Pelargonium* preparation (Conrad and Schulz, 2007).

Conrad et al. (2007c) summarized the adverse events for the period from 1990 until 2003. In this period, 109 million defined daily doses (DDD) of EPs® 7630 were marketed. In that time, 73 adverse events occurred spontaneously and 79 were reported in clinical trials, most of these 79 were rated as not being related to EPs® 7630. In 1 million DDD there were 0.67 spontaneous reports which in a treatment cycle of ten days maximum correspond to 1 report in 100.000 patients. Overall, only seven critical adverse events were reported between 1994 and 2003, and in all cases the causal relationship with EPs® 7630 was uncertain.

The Uppsala Monitoring Centre, in conjunction with the international pharmacovigilance program of the World Health Organization, received 34 case reports between 2002 and 2006 of allergic reactions to the ethanolic extract of *Pelargonium* root, all originating from Germany. In ten reports, concomitant use of other drugs was noted, but none of the concomitantly administered medication was recorded as being co-suspect. In 15 of the 34 reports, the description and timing of the event, notably the combination of a skin rash with itching, urticaria, angioedema and/or systematic involvement (e.g. dyspnoe, bronchospasm, diarrhea, tachycardia or circulatory failure) were suggestive of a Coombs and Gell
Type I acute hypersensitivity reaction. Two patients needed treatment for circulatory failure or anaphylactic shock, however, insufficient information was provided to determine if they had experienced anaphylactic shock. Further details of these two cases are provided as below:

Case report 1, concerning a 20-year-old woman, was reported by a dermatologist. After taking *Pelargonium* extract for the common cold the patient experienced life-threatening acute urticaria and circulatory failure, requiring emergency medical attention. The reaction subsided within 4 hours of initiation of corticosteroid and antihistamine treatment. The patient had not received any other drugs and a positive skin-pick test confirmed the causal involvement of *Pelargonium* extract.
Case report 2 was submitted by a pharmacist to the Medicines Committee of the German Pharmaceutical Association. The patient was a 71-year-old man who, within a day after first taking *Pelargonium* extract, experienced dyspnoe and swelling of the lips and tongue, necessitating hospital treatment (de Boer et al., 2007) (Patrick and Hickner, 2008).

Coumarins belong to the typical compounds of *Pelargonium* extract. They have been under scrutiny regarding the increased risk of bleeding and a possible impact on concomitant treatment with coumarin-type anticoagulants. To date, no case has been recorded in all the clinical trials that definitely proved any increased bleeding tendency that could be attributed to the treatment with *Pelargonium* extract (Kolodziej, 2008) (see below). One *in vivo* experiment affirmed this hypothesis (Koch and Biber, 2007).

According to the Cochrane Review, the available data from clinical trials with short-term therapies and results from uncontrolled post-marketing studies did not show an elevated risk of serious adverse events (Timmer et al., 2009).

According to a pharmacovigilance report from Italy, a patient suffering from congenital cardiac malformation, bronchial pneumonia, epilepsy, hypothyroidism, oligophrenia was taking a number of medicines, among them a *Pelargonium* product, and was diagnosed with acute hepatopathy. Although there was a positive rechallenge, taking into account the comorbidities and polymedication in case of this patient, a cause-effect relationship with *Pelargonium* could not be established. This case can only be considered as a signal. It is suggested that in case there is a hepatic disorder in the anamnesis, preparations containing no alcohol should be preferred.

5.4. Laboratory findings

The clinical trial carried out by Matthys et al. (2003) mentioned that the final assessment on day 7 of treatment included laboratory a test (leukocytes, erythrocyte sedimentation test, γ-GT, GOT, GPT, Quick's test and partial thromboplastin time-PTT). The mean values of all laboratory parameters did not change during the trial, neither for patients under EPs® 7630 nor for patients under placebo.

Chuchalin et al. (2005) examined the tolerability assessed by the results of laboratory tests including leukocytes and erythrocyte sedimentation rate, γ-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, Quick's test and PTT. Regarding the coagulation parameters, no differences between the two treatment groups were observed.

Matthys and Heger (2007) observed an increase of erythrocyte sedimentation rate (9.3% of patients in EPs® 7630 group vs. 9.2% of patients in placebo group) and a change of leukocyte count (3.7% of patients in EPs® 7630 group vs. 4.6% of patients in placebo group). These laboratory findings were due to the underlying infectious disease.

Matthys and Funk (2008) examined the liver function, leukocytes and erythrocyte sedimentation rate at baseline and at the end of treatment. No relevant differences were observed.

Bachert et al. (2009) reported that there was no clinically relevant change in any laboratory parameter and no clinically relevant individual deviations occurred in both treatment groups. No detailed information on laboratory test is available.

5.5. Safety in special populations and situations

One study examined the possible interaction between EPs® 7630 and antibiotics using penicillin V, as test substance. Twenty eight healthy test persons took for seven days 3 x 1 tablets Isocillin® 1.2 Mega alone (n=13) or in co-medication with 3 x 30 drops of EPs® 7630. The pharmacokinetic parameters of penicillin V on day 0 and day 7 were compared. Main target criteria were area under curve (AUC) and the maximum concentration of penicillin V in the plasma. The trial revealed no significant differences between the treatment with and without co-medication with EPs® 7630 (Conrad and Schulz, 2007).

On the basis of available non-clinical and limited clinical data, *Pelargonium* preparation does not influence either the blood coagulation parameters or the anticoagulant action of medicines (Koch and Biber, 2007) (Matthys et al., 2003) (Chuchalin et al., 2005).

To date, neither safety studies including women who are pregnant or breastfeeding, nor individuals with hepatic or renal disease, have not been performed.

No information is available on overdose, drug abuse and withdrawal. The ethanol content of *Pelargonium* preparations may influence the ability to drive.

5.6. Overall conclusions on clinical safety

On the basis of available safety data, the preparation of Pelargonii radix seems to be safe in the dosage administered in clinical and post-marketing trials.

6. Overall conclusions

Based on the available clinical data, the efficacy of Pelargonii radix in the symptomatic treatment of acute respiratory diseases, e.g. acute bronchitis, sinusitis, tonsillopharyngitis and common cold is not

proven properly. Based on the clinical evidence, the well-established use of Pelargonii radix is not acceptable in any of the investigated conditions.

According to the market overview, one extract (DER 1:8-10, extraction solvent: ethanol 11% m/m) of Pelargonii radix has been on the market for more than 30 years with the indication acute bronchitis (see product no. 4 in the German market overview, section 1.2). However, since this indication needs medical diagnosis and supervision, based on other traditional herbal medicinal products with the same composition in other member states, the following indication was accepted: symptomatic treatment of common cold.

There is no relevant information about the safety of *P. sidoides* during pregnancy and lactation. The administration of *Pelargonium* preparations in this patient group is not recommended.

Taking into consideration the favourable benefit/risk ratio (non-serious, minor and transient side effects in clinical trials) of *Pelargonium*, the publication of a traditional monograph is reasonable.

Annex

List of references