EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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 - revision

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) Dry extract, (DER 4-25:1), extraction solvent ethanol 11% (m/m)
Pharmaceutical form(s)	Herbal preparations in liquid or solid dosage forms for oral use.
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Note: A 'Review for specific reasons' (see RP EMA/HMPC/326440/2007 Rev.2) had been triggered by new scientific data available to the HMPC (re-evaluation of the Validity of the Bronchitis Severity Scale BSS, see meeting report May 2013 EMA/HMPC/301544/2013). Although no changes were introduced in the monograph, a public consultation was considered useful after careful new assessment of scientific data (in relation to the additional document made available since the primary assessment) as reflected in this revised draft AR (amendments to the relevant section 4). Interested parties are given the opportunity to comment before finalisation.

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This revised draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received solely on this assessment report without link to specified monograph sections. 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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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 were several *Pelargonium* species. Whereas *Pelargonium* species represent very popular ornamental plants in Europe, little was known of the medicinal practice with *Pelargonium*s in folk medicine in areas of southern Africa. Infusion of the roots of *Pelargonium sidoides* DC and *Pelargonium reniforme* Curt. have been used to treat coughs, chest problems including tuberculosis and gastrointestinal disorders such as diarrhea and dysentery. In addition, these plant materials were 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 from tuberculosis by the administration of a decoction of *Pelargonium* root prepared by a traditional healer (Helmstädter, 1996).

By comparative botanical as well as chromatographic studies it could be proved that two species i.e. *Pelargonium sidoides* or *Pelargonium reniforme* were used for the same purposes. 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 characterised 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)

Pelargonium root (Pelargonii radix is the dried, usually fragmented underground organs of *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt. Tannin content, expressed as pyrogallol, minimum 2% (Ph. Eur. 6.0, 2008). Standard scientific monograph compilations (Comission E, ESCOP and WHO monographs) do not include sections on *Pelargonium sidoides*.

- Herbal preparation(s)

Liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m)

Dry extract prepared from the liquid extract described above: DER 4-25:1, extraction solvent ethanol 11% (m/m)

- 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 functionalisation 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)

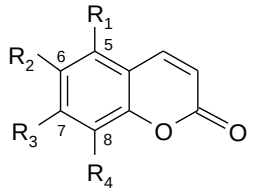
6,7-dihydroxy-derivative scopoletin
5,6,7-trisubstituted derivatives umckalin 5,6,7-trimethoxycoumarin
6,7,8-trioxygenated derivatives 6,8-dihydroxy-7-methoxycoumarine fraxetin
5,6,7,8-tetrasubstituted derivatives 6,8-dihydoxy-5,7-dimethoxycoumarine artelin
coumarin glycoside umckalin-7-β-glucoside
coumarin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

White *et al*. (2008) drew the attention to the uncontrolled harvest of at least 20 tons 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 plant 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 characterisation 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 characterisation of an unprecedented diterpene ester, designated as reniformin (Latte *et al*. 2007).

According to the European Pharmacopoeia, *Pelargonium* root has to contain not less than 2% of tannins, expressed as pyrogallol. The identification method of the European Pharmacopoeia is thin layer chromatography of the methanol root extract, but HPLC fingerprint analysis of *Pelargonium* extract was already achieved (Bladt and Wagner, 1988). Schnitzler *et al*. (2008) analysed 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 the constituents in *Pelargonium* extract (Figure 1.).

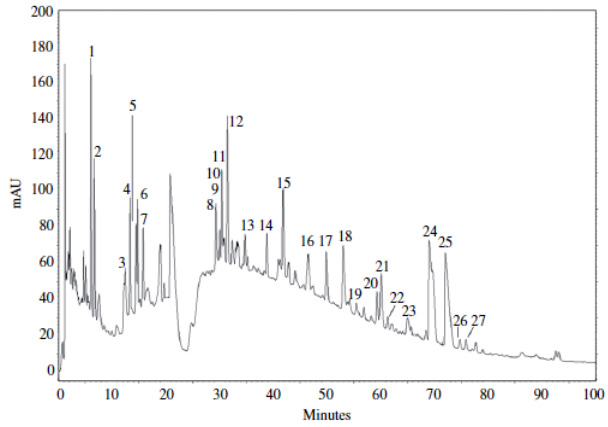


Figure 1: HPLC chromatogram of an aqueous P. sidoides extract at 260 nm (Schnitzler et al. 2008) (Assignment: 3- glucogallin, 8- fraxetin-7-O-glucoside, 11- catechin, 12- dihydroxy-coumarin-sulfate, 15- fraxetinsulfate, 16- monohydroxy-dimethoxycoumarin, 19,22- dihydroxy-dimethoxycoumarin, 23- dihydrokaemferol, 25- umckalin).

Special extract of *P. sidoides*. EPs® 7630 is a special 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).

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).

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

Austria

Traditional herbal medicinal products

Preparations:
1) Dry extract prepared from the liquid extract described below
2) Liquid extract (1:8-10), extraction solvent: ethanol 11% (m/m)

Pharmaceutical form:
1) Film-coated tablet
2) Oral liquid (1 ml = 21 drops)Posology:
all for oral use
1) > 12 years: 3 x daily 1 containing 20 mg extract
2) 1-5 years: 3 x daily 10 drops

6-12 years: 3 x daily 20 drops
> 12 years: 3 x daily 30 drops
10 g (= 9.75 ml) liquid contain 8 g extract

Indication:
1-2) Common cold

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

On the market since:
1) 2009
2) 2007

Belgium

Traditional herbal medicinal products

Preparations:
1-4) *Pelargonium* sidoides roots, liquid extract EtOH 11% (m/m) DER 1:8-10
5-6, 7) *Pelargonium* sidoides roots, dried extract EtOH 11% (m/m) DER 1:8-10

Pharmaceutical form:
1-4) Oral solution: 8 g extract per 10 g solution
5-6) Tablets: 20 mg extract per tablet
7) Syrup 0.25 g extract per 100 g syrup

Posology:
1-4) Adults & children > 12 years: 30 drops, 3 times daily
Children 6-12 years: 20 drops, 3 times daily
Children 1-5 years: 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

5-6) tablets
Adults & children > 12 years: 1 tablet 3 times daily (morning, noon, evening)
Children 6-12 years: 1 tablet, 2 times daily (morning, evening)
Tablets to be taken with some liquid; do not chew

3) syrup
Adults & children > 12 years: 7.5 ml, 3 times daily
Children 6-12 years: 5 ml, 3 times daily
Children 1-5 years: 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:
1-7) Common cold, exclusively based on traditional use

Legal status:
1-7) Registered traditional herbal medicinal product

On the market since:

1-5,7) 2009

6) 2013

Bulgaria

Directive 2001/83/EC

Preparations:

1) Liquid extract from Pelargonium sidoides DC, radix (Pelargonium root) (1 : 8 - 10) (EPs® 7630). The extraction agent is ethanol 11% (m/m).

Pharmaceutical form :

1) Oral drops, solution

Posology:

1) Adults and adolescents above 12 years: 30 drops 3 times daily.

Children 6 - 12 years: 20 drops three times per day.

Children 1 - 5 years: 10 drops three times per day.

Treatment duration should not exceed 3 weeks.

Indication:

1) Acute infections of the respiratory tract and the ear-nose-throat region such as bronchitis and sinusitis.

Legal status:

1) Authorised herbal medicinal product with marketing authorization according to Article 8(3) of Directive 2001/83/EC

Croatia

Preparation

1. 20 mg extract (as dry extract) from Pelargonium sidoides DC, radix (1 : 8–10). Extrakction solvent: ethanol 11 % m/m
2. 10 g (=9,75 ml) solution contains 8,0 g liquid extract from Pelargonium sidoides DC, radix (1 : 8–10). Extrakction solvent: ethanol 11 % m/m.

Pharmaceutical form:

1. film-coated tablet
2. oral solution

Posology:

Oral use, adults and adolescents older than 12 years: 1 tablet 3 times daily. Children 6-12 years: 1 tablet 2 times daily.

Oral use, adults and adolescents older than 12 years: 30 drops 3 times daily. Children 6-12 years: 20 drops 3 times daily.

Indication:

1-2) Traditional herbal medicinal product for the symptomatic treatment of common cold.

Legal status:

1-2) Traditional herbal medicinal product

On the market since:

1-2) 2013

Czech Republic

Herbal medicinal product with well-established use

Preparations:
1) Pelargonii sidoides extractum fluidum (1:8–10), extraction solvent ethanol 11% (m/m)
2) Pelargonii sidoidis extractum fluidum (1 : 8 – 10) extracted with ethanol 11% (m/m) (EPs 7630), dried 20 mg in 1 tablet
3) Pelargonii sidoidis extractum fluidum (1 : 8 – 10) extracted with ethanol 11% (m/m) (EPs 7630), dried 0,2506 g in 100 g of the product
4) Pelargonii sidoidis tinctura drug to extraction solvent ratio 1 : 10, extraction solvent ethanol 15 % (V/V) 80 g in 100 ml (= 100 g)

Pharmaceutical form:
1-4) Solution, oral drops
2) film-coated tablet
3) syrup

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

4) 1 ml of the product = 21 drops

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

Duration of use: 7–10 days

2) Adults and adolescents: 1 tablet 3 times daily; children 6 – 12 years : 1 tablet twice daily; children 1 – 5 years: 2.5 ml 3 times daily, use in children below 6 year is not recommended due to lack of adequate data

Duration of use: 7 – 10 days

3) Adults and adolescents: 7,5 ml 3 times daily; children 6 – 12 years : 5 ml 3 times daily; children 1 – 5 years: 2.5 ml 3 times daily, use in children below 1 year is not recommended due to lack of adequate data

Duration of use: 7 – 10 days

Indication:
1-4) Symptomatic treatment of acute bronchitis not requiring antibiotic therapy

Legal status:
1-4) Authorised herbal medicinal product

Since when is on the market:
1) 2008

2-3) line extension WEU

4) 2013 WEU

Germany

Herbal medicinal products with well-established use

Preparations:
1-3) Dry extract prepared from the liquid extract described below

4-9) Liquid extract (1:8-10), extraction solvent: ethanol 11% (m/m)

10-12) Dry extract of Pelargonii radix (4-25:1), extraction solvent: ethanol 11% (m/m)

Pharmaceutical form:
1-3) Film-coated tablet
4-9) Oral liquid
10-12) Syrup

Posology:
all for oral use
1-3) >12 years: 3 x daily 1 containing 20 mg extract

4-9)

1-5 years: 3 x daily 10 drops

6-12 years: 3 x daily 20 drops

> 12 years: 3 x daily 30 drops

10 g (= 9.75 ml) liquid contain 8 g extract

10-12)

0.2506 g / 100 g (93.985 ml)

1-6 years: 2.5 ml 3 times daily

7-12 years: 5 ml 3 times daily

>12 years: 7.5 ml 3 times daily

No longer than 3 weeks

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

10-12) Symptomatic treatment of acute bronchitis

Legal status:
1-9) authorised herbal medicinal products

On the market since:
1-3) 2009

4) at least since 1976
5-9) 2006

10-12) 2010

Herbal medicinal products with traditional use

Preparations:
1-4) Tincture of Pelargonii radix (1:8-10), extraction solvent: ethanol 15% (V/V)

5-8) Dry extract of Pelargonii radix (4-7:1), extraction solvent: ethanol 14% (V/V)

9) Tincture of Pelargonii radix (1:8-9), extraction solvent: ethanol 15% (m/m)

Pharmaceutical form:
1-4, 9) Oral liquid

5-8) Film-coated tablet 20 mg

Indication:

1-4, 5-8, 9) Symptomatic treatment of common cold

Posology:
1-4, 9) 16.48 g/20 ml (=20.6 g)

6-12 years: 20 drops

3 times daily

>12 years: 30 drops

3 times daily

No longer than 3 weeks

5-8) 6-12 years: 1

2 times daily

>12 years: 1

3 times daily

No longer than 3 weeks

Legal status: registered medicinal products

On the market since:
1-4, 5-8, 9) 2013

Hungary

Traditional herbal medicinal products

Preparations:
1) 10 g of oral solution containing 8 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 years: 3 x 30 drops daily
Children between 6-12 years: 3 x 20 drops

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

Legal status:
1) Registered traditional herbal medicinal product

On the market since:
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.

Latvia

Herbal medicinal product with well-established use

Preparations:
1) Liquid extract from Pelargonium sidoides DC roots (EPs 7630), extraction solvent: ethanol 11% (w/w), DER: 1:8-10. 10 g (9.75ml) of solution contains 8 g of extract

Pharmaceutical form:
1) Oral solution, drops

Posology:
Adults and children from 12 years – 30 drops 3 times per day; children 6-12 years: 20 drops 3 times per day; children 1-5 years: 10 drops 3 times per day.

Indication:
Use in case of acute un chronical infections, especially infections of respiratory tract and ear, throat and nose (bronchitis, sinusitis, tonsilitis, rhinopharingitis).

Legal status:
1) Authorised WEU herbal medicinal product

On the market since:
1) 2000

Lithuania

Herbal medicinal product with marketing authorization according to Article 8(3) of Directive 2001/83/EC

Preparations:

1) Pelargonium sidoides DC., radix liquid extract (from the roots of Pelargonium)

(extraction ratio 1:8 – 10)

Extraction agent: 11% ethanol (w/w).

Pharmaceutical form:

1) Oral drops, solution

Posology:

1) Adults and adolescents above 12 years: 30 drops 3 times daily.

Children 6-12 years: 20 drops 3 times daily.

Children 1 - 5 years: 10 drops 3 times daily.

Indication:

1) Symptomatic treatment of acute bronchitis, expectoration relief.

Legal status:

1) Authorised herbal medicinal product with marketing authorization according to Article 8(3) of Directive 2001/83/EC

On the market since:

1997

The Netherlands

Traditional herbal medicinal products

Preparations:

1) Pelargonium sidoides, radix, liquid extract (1:8 – 10) extraction solvent ethanol 11% (m/m)

2) Pelargonium sidoides, radix, dried extract (1:8 – 10) extraction solvent ethanol 11% (m/m)

Pharmaceutical form:

1. Oral liquid
2. Tablets
3. Syrup (2x)

Posology:

Oral drops containing per 10 g, 8 g extracts of Pelargonium sidoides roots (DER 1:8 – 10, extraction solvent ethanol 11% (m/m)

Oral: *adults and children from 12 years:* 30 drops, 3 times daily

Children from 6 to 12 years: 20 drops, 3 times daily

Children from 2 to 5 years: 10 drops, 3 times daily

Children from 1 year: 5 drops, 3 times daily

Tablets containing 20 mg of a dried extracts of Pelargonium sidoides roots (DER 1:8 – 10), extraction solvent ethanol 11% (m/m)

Oral: *adults and children from 12 years*

1 tablet, 3 times daily

Children from 6 to 12 years:

1 tablet, 2 times daily

Syrup containing 0.25 g dried extracts of Pelargonium sidoides roots (DER 1:8 – 10), extraction solvent ethanol 11% (m/m),

Oral: *adults and children from 12 years:* 7.5 ml syrup, 3 times daily

*Children from 6 to 12 years:*5 ml syrup, 3 times daily

*Children from 2 to 5 years:*2.5 ml syrup, 3 times daily

*Children from 1 year:*1.25 ml syrup, 3 times daily

Syrup for children containing 0.25 g dried extracts of Pelargonium sidoides roots (DER 1:8 – 10), extraction solvent ethanol 11% (m/m)), the finished product contains no alcohol

Children from 6 to 12 years: 5 ml syrup, 3 times daily

Children from 2 to 5 years: 2.5 ml syrup, 3 times daily

Children from 1 years: 1.25 ml syrup, 3 times daily

Indication:
Common cold, the use is exclusively based upon long-standing use.

Legal status:
Authorised traditional herbal medicinal product

On the market since:
1) June 2007
2) June 2009 (3x)

Romania

Herbal medicinal product with marketing authorization according to Article 8(3) of Directive 2001/83/EC

Preparations:

1) Extract of Pelargonium sidoides roots (1:8-10) 80 g/100g. Extraction agent 11%

ethanol (m/m).

Pharmaceutical form:

1) Oral drops, solution

Posology:

1) Adult and children above 12 years: 20-30 drops 3 times daily

Children 6 - 12 years: 10-20 drops 3 times daily.

Indication:

1) Adjuvant in treatment of upper and lower respiratory system acute and chronic

infections as well as bronchitis, sinusitis, tonsillitis, rhinopharyngitis

Legal status:

1) Authorised herbal medicinal product with marketing authorization according to Article 8(3) of Directive 2001/83/EC

On the market since:

2008

Slovakia

No products

Spain

Traditional herbal medicinal products

Preparations:

1) 10 g (= 9.75 ml) of oral solution contains 8 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 prepared by drying the liquid extract described above

Pharmaceutical form:

1) Solution, oral drops
2) Tablets

Posology:

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

On the market since:

1) 2009
2) 2009

Sweden

Traditional herbal medicinal products

Preparations:

1) Root, dry liquid extract, extraction solvent: ethanol 11% (m/m). DER genuine 1:8-10 (liquid extract), DER 4-25:1 (dried liquid extract), DER manufacturing 0.7-4.5:1.
2) Root, liquid extract, extraction solvent: ethanol 11% (m/m). DER genuine 1:8-10
3) *Pelargonium sidoides* (pelargonium), root, liquid extract (DER 1:8-10) extraction solvent ethanol 15 % (v/v

Pharmaceutical form:
1) Film-coated tablet
2-3) Oral drops, solution

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

3) Adolescents over the age of 12 years, adults and elderly: 1186 mg (=1.15 ml) liquid extract 3 times daily
Children between 6-12: years: 793 mg (= 0.78 ml) liquid extract 3 times daily

Indication:
1-3) Traditional herbal medicinal product for symptomatic relief of the common cold

Legal status:
1-3) Registered traditional herbal medicinal product

On the market since:
1-2) 2009-05-11
3) 2011

United Kingdom

Traditional herbal medicinal products

Preparations:
1) Root, *liquid* extract, extraction solvent: ethanol 15% (V/V) DER genuine (1:8-10)
2) Root, dry extract, extraction solvent: 14% (V/V), DER genuine (4-7:1)
3) root, dried liquid extract, extraction solvent: ethanol 11 % (w/w), DER genuine (1:8-10)
4) Root, dry extract, extraction solvent: 11% ethanol (w/w), DER genuine (1:8-10)
5) Root, *liquid* extract, extraction solvent: 11% ethanol (w/w), DER genuine (1:8-10)

Pharmaceutical form:
1) Oral drops, solution
2) Film-coated tablet
3) Syrup
4) Film-coated tablet
5) Oral drops, solution

Posology:

1. Adults, Elderly and children over 12 years: 30 drops three times per day
   Children from 6 to 12 years: 20 drops three times per day
   The use in children under 6 years of age is not recommended

2. Adults, elderly and adolescents above 12 years of age: Take 1 tablet three times daily
   The use in children under 12 years of age is not recommended

3. Adults, elderly and adolescents above 12 years of age: Take 1 tablet three times daily
   The use in children under 12 years of age is not recommended
4. Adults and adolescents over 12 years of age: Take 1 tablet three times daily
   The use in children under 12 years of age is not recommended
5. Adults and adolescents over the age of 12: Take 30 drops three times per day
   Children aged between 6-12 years: Take 20 drops three times per day.
   The use in children under 6 years of age is not recommended

Indication

1-5) Traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including common cold, such as sore throat, cough and blocked or runny nose, based on traditional use only.

Legal status

1-5) Registered traditional herbal medicinal product

On the market since:

1) 27/10/2011
2) 02/06/2011
3) 02/06/2011
4) 01/09/2011
5) 10/02/2011

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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 registered or authorised products
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Hungary	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or

Member State	Regulatory Status				Comments
					authorised products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Latvia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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:	
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 registered or authorised products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No response
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No registered or authorised products
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Databases SciFinder, Science Direct, Web of Science and PubMed were searched using the terms [*Pelargonium*], [EPs® 7630] and [coumarin] upto the end of August 2015. Handbooks and textbooks were also used.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the European Union

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 (TB) in the clear mountain air. 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".

In the early 1900s, Stevens' Consumption Cure was a 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 favour of BMA and he was ordered to pay 2000 pounds of legal cost.

After the First World War, Stevens continued to promote his *Pelargonium*-containing preparation. 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).

Primarily, 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 Bladt, at the University of Munich, used ethnobotanical, comparative botanical and chromatographic techniques to show that the roots originated from the *Geraniaceae* species *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. *Pelargonium* received a full market authorisation 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 the European Pharmacopoeia in 2008.
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 preparations from *Pelargonium* radix is available from clinical trials and manufacturers. 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

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. In accordance with the Directive 2004/24/EC, the native dry extract equivalent to the above mentioned liquid extract (dry extract, DER 4-25:1, extraction solvent ethanol 11% (m/m)) is also included in the traditional use monograph.

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.

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 (containing 20 mg dry extract/tablet) are prescribed for adults and 3 x 20 drops or 2 x 1 tablets for children between 6-12 years of age. The most recent posology of the reference product with the confirmed 30 years of application is as follows:

1-5 y: 3 x daily 10 drops
6-12 years: 3 x daily 20 drops
> 12 years: 3 x daily 30 drops

Although there exist clinical studies involving children under the age of 6 years, there is no stratification for age when assessing the safety (exact number of adverse events in this age group is not known) of the treatment. Hence, the confirmation of safety under 6 years was considered insufficient to allow the application in this age group in the monograph.

10 g of the preparation contains 8 g Pelargonii radix extract (DER: 1:8-10), extraction solvent: ethanol 11% (m/m).

Taking into account the density of the finished product (1.018 – 1.038, mean 1.028 g/ml), the density of the liquid extract (0.975 – 1.000, mean 0.9875 g/ml) and the drop count (20-21 drops/ml finished product):

30 drops finished product = 1.4286-1.5 ml = 1.4686-1.542 g = 1.1749-1.2336 g native extract= 1.1897-1.2492 ml native extract.

20 drops finished product = 0.9524-1 ml = 0.9790-1.028 g = 0.7832-0.8224 g native extract= 0.7932-0.8328 ml native extract.

Based on this, and taking into account safety aspects as well, the posology of Pelargonii radix containing products is as follows:

Adolescents, adults and elderly:

1.19-1.25 ml liquid extract, 3 times daily.

20 mg dry extract, 3 times daily

Children between 6-12 years:

0.79-0.83 ml liquid extract, 3 times daily.

20 mg dry extract, 2 times daily

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. However, the antibacterial activity of these compounds is significantly weaker compared to antibiotics. The aqueous fraction 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 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/ml, *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 colonisation 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* (control: pentostam). 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, apart from the coumarin samples, all the *Pelargonium* extracts (EC_{50} <0.1-3.3 microg/ml), gallic acid (EC_{50} 4.4 microg/ml) and its methyl ester (EC_{50} 12.5 microg/ml) significantly reduced the intracellular survival of *L. donovani* amastigotes within murine macrophages. The samples exhibited no or negligible host cell cytotoxicity. These findings indicated that the samples acted indirectly against *Leishmania* 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 (control: LPS). 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 (3, 10, and 30 µg/ml). 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. The IC_{50} for *P. sidoides* extract was determined from dose–response curves at 0.00006% and 0.000005% for HSV-1 and HSV-2, respectively, and a dose-dependent activity of the extract could be demonstrated. Acyclovir showed the maximum antiviral activity when added at a concentration of 22.5 mg/ml during the replication period with inhibition of the viral replication of more than 98% for both herpes viruses. 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. The animals were treated with LPS at 100, 200 or 400 µg/kg bw and 1, 2 or 3 h later placed in the light compartment of the light-dark-box for 3 min. For main experiments a dose of 400 µg/kg LPS administrated 2 h for the behavior experiment was used. Control animals received an oral administration of vehicle or the

high dose of EPs® 7630 (400 µg/kg bw) and an i.p. injection of saline. Treated animals received EPs® 7630 and an i.p. injection of LPS.

Neugebauer *et al*. (2005) demonstrated that EPs® 7630 significantly and dose-dependently (1-100 µ g/ml) 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 metabolised 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 metabolise coumarin by the 3,4-epoxidation and possibly other pathways leading to formation of toxic o-HPAA (Egan *et al*. 1990) (Lake, 1999).

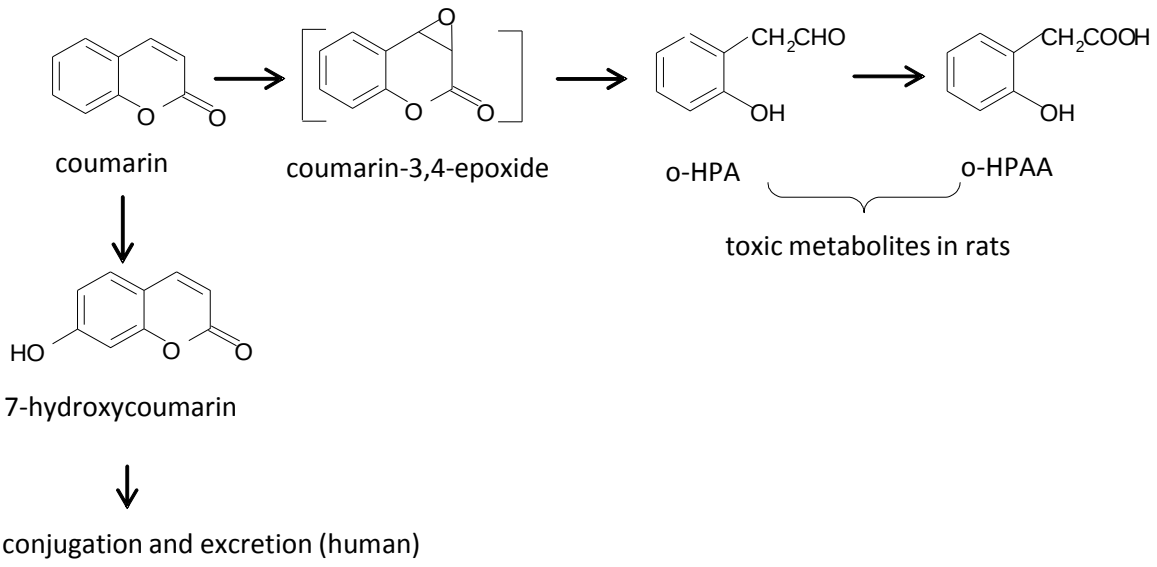


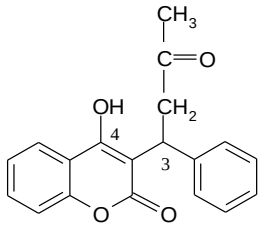
Figure 2: Some pathways of coumarin metabolism (o-HPA = o-hydroxyphenylacetaldehyde; o-HPAA = o-hydroxyphenylpropionic acid) (Lake, 1999)

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 (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 preparations from Pelargonium radix

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-1 and 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) published the results of 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 (no data on duration) 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. However, most of the studies have no controls (at least they are not mentioned) therefore the relevance of these results is not clear. Moreover the concentration of *Pelargonium* compounds in the body is not known.

Although there is limited knowledge about pharmacokinetic parameters and toxicological data of *Pelargonium* extract, the results of non-clinical trials raise no safety concern.

Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been published.

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

EPs® 7630 solution has been on the market at least since 1976, but the first average daily dosage of *Pelargonium sidoides*-radix, 3 x 30 drops, was established only empirically as usual at phytotheraputic preparations.

Between 26-Nov-2001 and 09-May2003 the efficacy and safety of two different doses of EPs® 7630 solution was compared to placebo in a prospective, randomised, double blind, multicentre, phase III, four parallel groups trial in adult patients with acute bronchitis (Romberg-2004d-UM037-clinical trial report). 1792 patients were screened and 637 patients were enrolled into the trial by 40 investigational sites: 13 sites in Germany, 14 in Poland and 13 in Ukraine.

All 637 included patients were randomised to one of the four treatment groups: 214 patients to EPs® 7630 solution 3 x 30 drops, 107 patients to the placebo 3 x 30 drops group, 210 patients to the EPs® 7630 solution 3 x 45 drops group and 106 patients to the placebo 3 x 30 drops group. The results of the two placebo groups were considered as pooled data of all patients that received placebo. Placebo was matched to EPs® 7630 solution with regard to colour, smell, taste and viscosity.

EPs® 7630 solution as well as placebo was administered over a period of up to 14 days: drops p.o. 3 times daily, 30 minutes prior to the meal.

Follow–up examinations were scheduled between Day 3-5, on Day 7 and on Day 14. In case of fever ≥39°C paracetamol tablets were allowed until Day 7.

During the whole period, the patients had to fill a patient diary.

The inclusion criteria were: age 18-60, acute bronchitis with productive cough since ≤72 h. BSS ≥8 points.

Exclusion criteria were chronic lung diseases, any clinical characteristic suggesting pneumonia, concomitant diseases of upper respiratory tract, treatment with antibiotics, ACE-inhibitors, beta-blockers, bronchodilatators or glucocorticoids during the past 4 weeks prior to enrolment or previous treatment with secretolytics, mucolytics, antitussives, or analgesics within 7 days prior to inclusion into the trial.

Baseline characteristics:
The demographic and baseline data were either well balanced or slightly different between treatment groups. As the differences were minor and in varying favour of the treatment groups, a clinically relevant difference in the overall health condition of the patients in any treatment group could not be deduced.

At baseline, overall BSS was 10.4±1.7 [10.0]. The BSS was on average the same in all treatment groups.

The number of patients with at least severe intensity of cough, sputum, rales/rhonchi, chest pain during coughing and dyspnoea was higher or equal in both EPs® 7630 groups than in the placebo group.

Assessor's comment:
Unfortunately the Clinical report provided by the Company does not contain the Appendix with the concrete baseline data of bronchitis specific symtoms. Futhermore it is not known whether statistical

analyses of the baseline characteristics between groups were done or not. In some cases the difference can be clinically relevant for example:

"Predominance of females differed between treatment groups with 70.1% of patients in the EPs® 7630 3 x 30 group, 76.2% of patients in the EPs® 7630 3 x 45 group and 73.2% of patients in the placebo group. Limitation of daily activities: On Day 0, the rating of deficiency of activities was in the majority of patients 50% or 25%. A deficiency of 50% was recorded 119/24 patients (55.6%) of the EPs® 7630 3 x 30 group, 114/210 patients (54.3%) of EPs® 7630 3 x 45 and 98/213 patients (46.0%) of the placebo group. A deficiency of 25% was recorded by 63/214 patients (29.4%) of the EPs® 7630 3 x 30 group, 61/210 patients (29.0%) of EPs® 7630 3 x 45 and 87/213 patients (40.8%) of the placebo group."

Criteria for Evaluation

Efficacy:
The primary outcome criterion was the change of Bronchitis Severity Score (BSS) from baseline to Day 7 (arithmetic mean, Day 7 - minus Day 0). The BSS total score consists of the five symptoms coughing, sputum production, pulmonary rales/rhonchi at auscultation, chest pain while coughing and dyspnoea, which are the most important features associated with acute bronchitis, rated on a scale from 0 (not present, mild, moderate, severe, very severe) to 4 and leading to a maximum total score of 20 points.

As secondary efficacy variables three response criteria were determined: (1) BSS total score less than 3 points on Day 7, (2) decrease in BSS total score of at least 7 points from day 0 to Day 7, and (3) combination of criteria 1 and 2.

Other 11 secondary outcome criteria were also determined: treatment outcome acclording to the Integrative Medicine Outcome Scale (IMOS), onset of treatment effect, consumption of paracetamol, change of the individual symtoms of BSS and futher symptoms, time to resolution of cough and sputum production, genaral well-being of the patients, patients' health status, limitation of daily activities, inability to work, satisfaction with the treatment.

Safety:
Safety outcome criteria were the followings:

- number, kind and severity of adverse effects
- tolerability based on verbal 4-point rating scale assessed by both the investigator and the patients.

Statistical method:
The trial was conducted according to a group sequential adaptive design with two interim analyses. The comfirmatory comparison of the treatment groups concerning the primary efficacy variable was performed using a one-factorial analysis of covariance with factor treatment and the baseline value as covariate. Descriptive statistical methods were used to analyse secondary and furher variables. The last-obsevation-carried-forward (LOCF) method was used when patients discontinued the trial prior to Day 7 and data were missing at Day 7. The analysis of the trial was based on the intent-to-treat (ITT) sample. In addition, the per-protocol (PP) sample was analysed.

Based on results of previous studies, the average decrease of BSS from baseline was expected to be 4 points under placebo and 6 points under EPs® 7630. A difference of 1 point was considered clinically relevant in the patient population of this trial. With a sample size of 250 patients in each treatment group, the trial was estimated to have power of 80% to detect a difference between groups of 1 point in the change from baseline of BSS (t-test for independent samples, α=0.025 one sided).

Assessor's comment:
A difference of 1 point between treatment groups cannot be considered clinically relevant.

Results

Duration of treatment was shorter in the placebo group as compared to EPs® 7631 groups (EPs® 7630 3 x 30: 14.0 days (mean), EPs® 7630 3 x 45: 14 days, placebo: 4.0 days) beause more patients of the placebo group terminated the treatment with the investigational mediction prematurely. 344 patients terminated the trial prematurely. 80 patients in the EPs® 7630 3 x 30 group, 75 patients in the EPs® 7630 3 x 45 group and 189 patients in the placebo group.

Asssessor's comment:
344 of 637 (54%) patients terminated the trial prematurely: 80 of 214 (37.3%) patients in the EPs® 7630 3 x 30 group, 75 of 210 (35.7%) patients in the EPs® 7630 3 x 45 group and 189 of 213 (88.7%) patients in the placebo group.

The major reasons for withdrawal were lack of efficacy and being free of symptoms. Lack of efficacy was reported for 197/344 patients predominantly belong to the placebo group (14/80 (17.5%) patients in the EPs® 7630 3 x 30 group, 6/75 (8.0%) in the EPs® 7630 3 x 45 group, and 177/189 (93.7%) patients in the placebo group) which was documented mainly on Day 3-5. Being free of symptoms was reported for 126/344 (36.6/%) patients which was mostly reported for patients in both EPs® 7630 groups [58/80 (72.5%) patients in the EPs® 7630 3 x 30 group, 63/75 (84.0%) in the EPs® 7630 3 x 45 group and 5/ 189 (2.65 %) patients in the placebo group], which was documented mainly on Day 7.

Adverse effects were reason of withdrawals in 6 cases in the EPs® 7630 3 x 30 group, in 3 cases in the EPs® 7630 3 x 45 group and in 5 cases in the placebo group.

Assessor's comment:
By Day 5, 164 of 213 (77%) patients in the placebo group were withdrawn from the trial.

Efficacy:
On Day 7 (LOCF) BSS decreased more pronounced in both EPs® 7630 groups -7.1±2.8[-8.0] points (3 x 30) and 7.6± 2.5[-8.0] points (3 x 45) than in the placebo group -0.8±2.8 [0.0] points which was statistically highly signifiacant for the comparisons of both EPs® 7630 groups vs. placebo ($p<0.0001$).

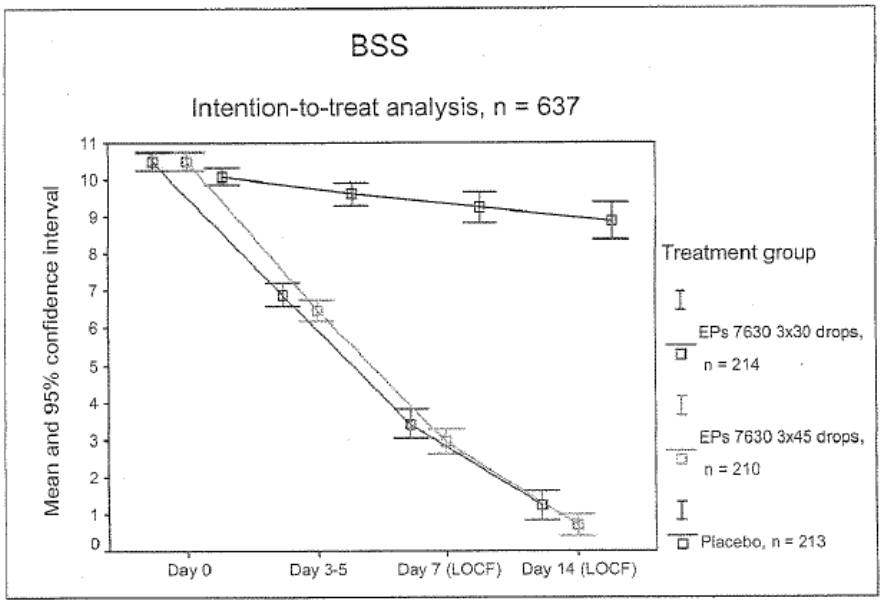


Figure 4: arithmetic means and corresponding two-sided confidence intervals over time (cited from Romberg-2004d-UM037-clinical trial report)

Per-protocol analysis shows similar results.

Assessor's comment:

Unfortunately no table with the numerical changes from baseline to day 14 was provided.

Secondary Outcome Criteria:

Response criterion no.1: BSS on Day 7 below 3 points.

Response criterion no.2: decrease of BSS (Day 7 minus Day 0) of at least 7 points.

Response criterion no. 3: patients meets criterion 1 and 2. i.e. BSS on Day 7 below 3 points and decrease of BSS (Day 7 minus Day 0) of at least 7 points.

Response rates were much higher in both EPs® 7630 groups as compared to the placebo group and the response rates in the EPs® 7630 3 x 45 group were always higher as compared to the EPs® 7630 3 x 30 group. The specific response rate of the EPs® 7630 3 x 30 and the EPs® 7630 3 x 45 group were 34.1% and 38.1% (criterion no.1) 65.9% and 73.8% (criterion no.2) and 33.2% and 38.1% (criterion no.3%) respectively. The related response rates for the placebo group were 5.2%, 8.0% and 3.8%, respectively.

Treatment outcome (IMOS):

Recovery rates as assessed by the investigator:

The cumulative recovery rates after 3-5 Days (LOCF) were 1/214 patients (0.5%) for the EPs® 7630 3 x 30 group, 0/210 patients (0.0%) for the EPs® 7630 3 x 45 group and 0/213 patinets (0.0%) for the placebo group.

The corresponding recovery rates after 7 days (LOCF) were 50/214 patients (23.4%) for the EPs® 7630 3 x 30 group 58/210 patients (27.6%) for the EPs® 7630 3 x 45 group and 4/213 patinets (1.9%) for the placebo group.

The corresponding recovery rates after 14 days (LOCF) were 156/214 patients (72.9%) for the EPs® 7630 3 x 30 group, 168/210 patients (80.0%) for the EPs® 7630 3 x 45 group and 16/213 patinets (7.5%) for the placebo group.

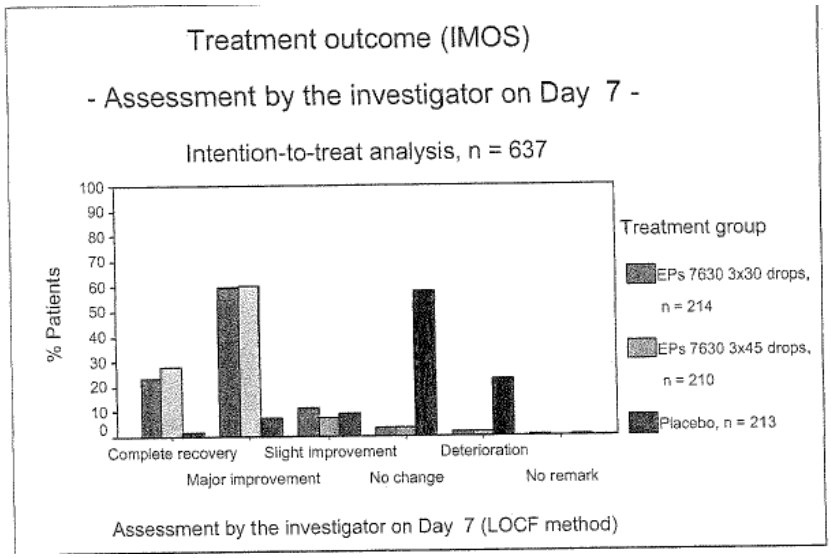


Figure 5: treatment outcomes (IMOS) – assessment of the investigator on Day 7 (ITT) (cited from Romberg-2004d-UM037-clinical trial report)

Similar evaluation was given by the patients as well.

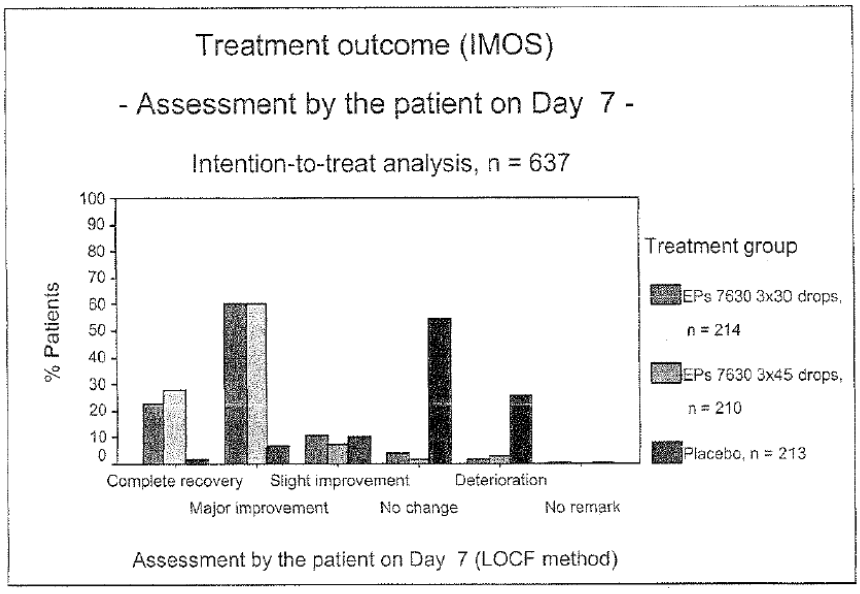


Figure 6: treatment outcome (IMOS) – assessment by the patient on Day 7 (ITT) (cited from Romberg-2004d-UM037-clinical trial report)

Change of the individual Symptoms of BSS:

Cough:

On Day 7 (LOCF) cough disappeared in 51/214 patients (23.8%) of EPs® 7630 3 x 30 group, 57/210 patients (27.1%) of EPs® 7630 3 x 45 group and 4/213 (1.9%) of placebo group. The symptom improved in 143/214 patients (66.8%) of the EPs® 7630 3 x 30 group, 140/210 patients (66.7%) of the EPs® 7630 3 x 45 group and 34/213 patients (16%) of the placebo group. No change or deterioration of cough was documented in 20/214 patients (9.3%) of the EPs® 7630 3 x 30 group, 13/210 (6.2%) EPs® 7630 3 x 45 group and 175/213 patients (82.2%) of the placebo group.

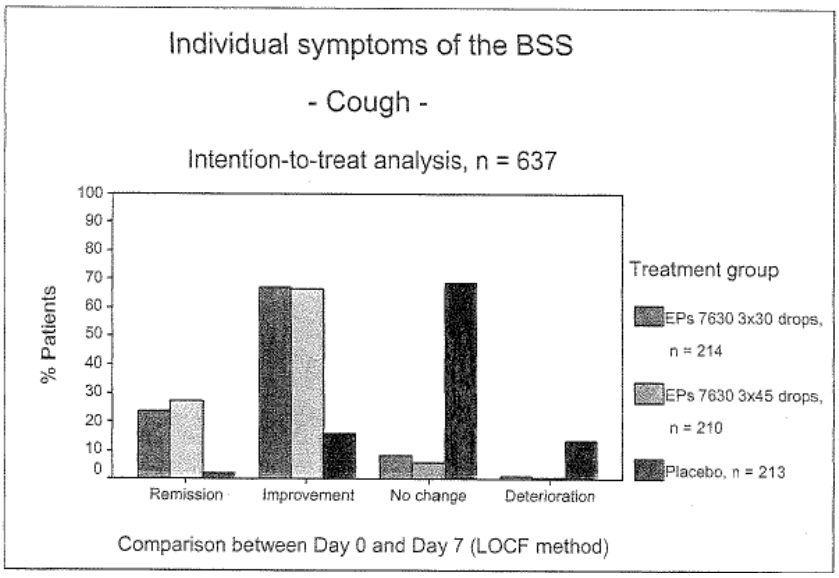


Figure 7: Clinical finding (individual symptoms of BSS) – cough (ITT) (cited from Romberg-2004d-UM037-clinical trial report)

Assessor's comment:

Unfortunately no table with the numerical changes from baseline to day 14 was provided.

Sputum:

On Day 7 (LOCF), sputum disappeared in 57/212 patients (26.9%) of the EPs® 7630 3 x 30 group, 67/209 patients (32.1%) of the EPs® 7630 3 x 45 group and 8/213 patients (3.8%) of the placebo group.

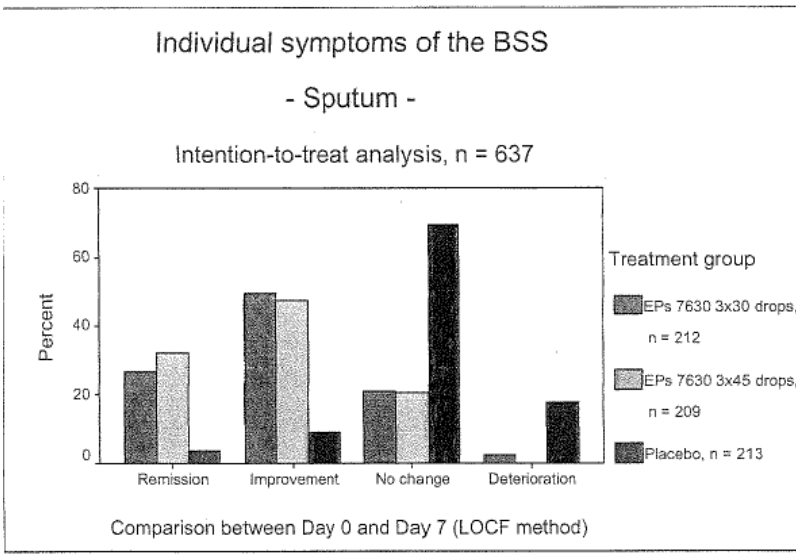


Figure 8: Clinical finding (individual symptoms of BSS) – sputum (ITT) (cited from Romberg-2004d-UM037-clinical trial report)

Assessor's comment:

Unfortunately no table with the numerical changes from baseline to day 14 was provided.

The improvement of the other symptoms of BSS (pulmonary rales/rhonchi at auscultation, chest pain while coughing and dyspnoea) showed the same tendency.

Inability to work:

At baseline, 184 patients in the EPs® 7630 3 x 30 group, 174 patients in the EPs® 7630 3 x 45 group and 168 patients in the placebo group were unable to work. Thereof, 144/184 patients (78.3%) in the EPs® 3 x 30 group, 136/174 (78.2%) in the EPs® 7630 group 3 x 45 group and 18/169 patients (10.7%) in the placebo group were fit again on Day 7 (LOCF).

Other secondary efficacy parameters showed the same tendency as well. The results of the secondary outcome criteria of EPs® 7630 3 x 45 group in comparison with the EPs® 7630 3 x 30 group were either comparable or slightly different and of no clinical relevance.

Safety

The number of reported adverse events (AE) was higher in the the EPs® 7630 3 x 30 group (23 AEs) and the EPs® 7630 3 x 45 group (28 AEs) respectively, as compared to the placebo groups (16 AEs). The incidence of AEs was 9.3%, 12.9% and 7.0% patients (EPs® 7630 3 x 30 group, EPs® 7630 3 x 45 group, placebo groups). No serious adverse events occurred during the trial.

The most frequently coded organ class was "gastrointestinal disorders" (EPs® 7630 3 x 30 group: 6/15 (40%), EPs® 7630 3 x 45 group 9/15(60%), placebo : 6/16 (37.5%)) followed by the organ classs of "respiratory, thoracic and mediastinal disorders (EPs® 7630 3 x 30 group: 3/9 (33.3%), EPs® 7630 3 x 45 group 6/9(66.7%), placebo: 3/16 (18.8%)), "nervous sytem disorders" (EPs® 7630 3 x 30 group: 3/9 (33.3%), EPs® 7630 3 x 45 group 6/9 (66.7%), placebo: 0/16 (0%)), infections and infestations (EPs® 7630 3 x 30 group: 3/6 (50%), EPs® 7630 3 x 45 group 3/6 (50%), placebo: 3/16 (18.8 %)) and "ear and labyrinth disorders" EPs® 7630 3 x 30 group: 3/5 (60%), EPs® 7630 3 x 45 group 2/5 (40%), placebo: 0/16 (0%)).

Assessor's overall conclusion on the study:
According to the American Academy of Family Physicians symtoms of acute bronchitis is a clinical term implying a self-limited inflammation of the large airways of the lung that characterized by cough without pneumonia. Viruses are usually considered the cause of acute bronchitis. During the first few days of infection, thy symptoms of mild upper respiratory infections cannot be distinguished from those of acute bronchitis. However with acute bronchitis, coughing persists more than 5 days and typically persists 10-20 days.

Duration of this study was 14 days but the comparison of the efficacy between treatment groups and the placebo groups was already made on day 7. According to the authors it was claimed, that "The duration of treatment of 7 days chosen for this trial is adequate because of natural course of underlying disease." Considering the above-mentioned, it does not seem to be justified to carry out a 14-day study with the assessment of efficacy on day 7. 344 of 637 (54%) patients terminated the trial prematurely: 37.3%, 35.7% and 88.7% of the patients in the EPs® 7630 3 x 30, 3 x 45 and placebo group, respectively. The major reasons for withdrawal were lack of efficacy and being free of symptoms.

Lack of efficacy was reported for 197/637 (30.9%) patients predominantly belong to the placebo group (6.5%, 2.8% and 83.1% of the patients in the EPs® 7630 3 x 30, 3 x 45 and the placebo group, respectively), which was documented mainly on day 3-5.

Being free of symptoms was reported for 126/637 patients (19.8%) which was mostly reported for patients in both EPs® 7630 groups (27.1%, 30.0% and 2.3% of the patients in the EPs® 7630 3 x 30, 3 x 45 and placebo group, repectively, which was documented mainly on day 7. Somehow these data for being free of symtoms are not in line with the data provided for "treatment outcome (IMOS)": the corresponding recovery rates after 7 days (LOCF) were 50/214 patients (23.4%) for the EPs® 7630 3 x 30 group, 58/210 patients (27.6%) for the EPs® 7630 3x45 group and 4/213 patinets (1.9%) for the placebo group. The difference between the decrease of symtoms score in the treatment groups and the placebo group seems not only statistically significant but clinically as well. On day 7 (LOCF) BSS decreased more pronounced in both EPs® 7630 groups -7.1±2.8 [-8.0] points (3x30) and 7.6± 2.5 [-8.0] points (3x45) than in the placebo group -0.8±2.8 [0.0] points which was statistically highly signifiacant for the comparisons of both EPs® 7630 groups vs. placebo (p<0.0001). Difference is 6.3 (7.1-0.8) for EPs® 7630 30 x 30 groups and 6.8 (7.6-0.8) for the EPs® 7630 3 x 45 group.

However, the problem is the big number of withdrawals. The report does not give an explanation for it. There are no data about the results of the visits on day 14. Since there are lots of unanswered questions in this study thus its result cannot be considered.

Dose finding study with EPs 7630 film-coated tablet:

Another dose-finding, randomised, placebo controlled, double-blind, multi-center study sponsored by the producer study was carried out to compare three different doses of EPs® 7630 film-coated tablet 10, 20, 30 mg versus placebo in the treatment of adults suffering from acute bronchitis (Malek *et al*., 2007c Study Report No: 701003.01.003; published in: Matthys *et al*., 2010a; Matthys *et al*., 2010b; Schulz, 2008a). This clinical trial was conducted at 16 study centers in the Ukraine between February and April 2006. EPs® 7630 extract consisted of a dried 11% w/w ethanolic root extract (1:8-10).

405 adults (>18 years old) were included in the study. The main criteria for inclusion were that the starts of symptoms of acute bronchitis had to be ≤48 hours prior to inclusion the study and total score of bronchitis–specific symptoms had to be ≥5 points at screening. The patients were randomized into a placebo group or 1 of 3 treatment groups: 30, 60, or 90 mg EPs® 7630/day. Following a screening visit, the patients took their assigned treatment 30 minutes before meals 3 times daily for 8 days.

The same statistical method was used as in the study mentioned above.

Comparison of treatment groups with respect to gender, age and body max index (BMI) showed no difference between the treatment groups (see Table 3).

Base-line parameters

Demographic and anthropometric data

(FAS; sex: absolute (relative) frequency and age, weight, height and BMI: mean (SD), median)

	Placebo (n = 102)	EPs® 7630 30 mg (n = 102)	EPs® 7630 60 mg (n = 101)	EPs® 7630 90 mg (n = 100)
Sex				
male	39 (38.2%)	32 (31.4%)	24 (23.8%)	28 (28.0%)
female	63 (61.8%)	70 (68.6%)	77 (76.2%)	72 (72.0%)
Age [years]	38.49 (12.58)	40.26 (12.16)	41.79 (13.20)	38.80 (13.69)
	39.0	42.0	44.0	38.5
Weight [kg]	74.05 (14.71)	72.39 (11.99)	73.33 (12.68)	71.51 (12.54)
	72.0	72.0	74.0	70.0
Height [cm]	169.92 (7.34)	168.80 (7.22)	168.50 (8.34)	169.12 (7.75)
	170.0	168.5	168.0	168.0
BMI [kg/m^2]	25.56 (4.46)	25.40 (3.93)	25.82 (4.06)	25.00 (4.10)
	24.6	25.5	25.8	24.1

Table 3: Demographic and anthropometric data (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003 (FAS: full analysis set))

Assessor's comment:

More male patients were in the placebo group (38.2%) than in the treatment groups (31.4% for 30 mg, 23.8 % for 60 mg and 28.0% for 90 mg of EPs® 7630). Its possible consequences were not discussed by the authors.

The difference in smoking habits between the treatment groups was statistically significant (PFAS=0.0018): 15/102 (14.7%), 26/102 (25.5%), 7/101 (6.9%) and 13/100 (13%) patients were smokers and 75/102 (73.5%), 68/102 (66.7%), 79/101 (78.2%) and 83/100 (83.0%) patients were non-smokers in the placebo, EPs® 7630 30 mg, 60 mg and 90 mg group.

Assessor's comment:

In the original article about this dose-finding study Matthys et al. (2010b) stated that the evaluation of demographic and anthropometric data as well as smoking habits revealed no significant differences between the four groups. This is a statement without argumentation and is not in line with the clinical report.

In the FAS (full analysis set) as well as in the PPS (per protocol set), symptoms were slightly more prominent and BSS was slightly higher in the EPs® 60 mg and 90 mg group compared to placebo at baseline. This small difference was statistically significant regrading the BSS total score at baseline for EPs® 90 mg group. No statistically significant baseline differences were observed regarding the single symptoms.

	FAS (n = 405)			
	Placebo (n = 102)	EPs® 7630 30 mg (n = 102)	EPs® 7630 60 mg (n = 101)	EPs® 7630 90 mg (n = 100)
Bronchitis-specific symptoms (BSS, total score)	8.2 (1.7) 8.0	8.2 (1.7) 8.0	8.6 (1.7) 8.0	8.7 (1.8) 8.0
Individual bronchitis-specific symptoms:				
Coughing	2.6 (0.7) 2.5	2.7 (0.7) 3.0	2.8 (0.6) 3.0	2.7 (0.7) 3.0
Sputum	0.7 (0.8) 1.0	0.7 (0.8) 1.0	0.8 (0.9) 1.0	0.8 (0.9) 0.0
Pulmonary rales at auscultation	1.9 (0.6) 2.0	1.9 (0.7) 2.0	2.0 (0.6) 2.0	2.0 (0.7) 2.0
Chest pain while coughing	1.9 (0.6) 2.0	1.8 (0.7) 2.0	1.8 (0.7) 2.0	2.0 (0.8) 2.0
Dyspnoea	1.1 (0.7) 1.0	1.0 (0.6) 1.0	1.1 (0.7) 1.0	1.2 (0.7) 1.0

Table 4: Outcome measures at baseline (Day 0) (mean (SD), median, FAS: Full analysis set) (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003)

Efficacy

The primary efficacy variables were changes in bronchitis symptoms total score (BSS) from Day 0 to Day 7.

BSS total score (mean (SD), median; LOCF)

		FAS (n = 405)			
		Placebo (n = 102)	EPs® 7630 30 mg (n = 102)	EPs® 7630 60 mg (n = 101)	EPs® 7630 90 mg (n = 100)
Baseline	Day 0	8.2 (1.7) 8.0	8.2 (1.7) 8.0	8.6 (1.7) 8.0	8.7 (1.8) 8.0
	Day 3-5	7.5 (2.0) 7.0	6.4 (2.1) 7.0	5.5 (1.7) 6.0	5.8 (2.0) 6.0
	Day 7 (LOCF)	5.5 (2.1) 5.0	3.9 (2.0) 4.0	2.4 (1.6) 2.0	2.4 (1.6) 2.0
Change	Day 0 – Day 7 (LOCF)	2.7 (2.3) 2.5	4.3 (1.9) 4.0	6.1 (2.1) 6-0	6.3 (2.0) 6.0

Table 5: changes in BSS from Day 0 to Day 7 as primary outcome measures (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003

Between day 0 and day 7, the mean BSS score decreased by 2.7 +/- 2.3 (placebo), 4.3±1.9 (30 mg group), 6.1±2.1 (60 mg group), and 6.3±2.0 points (90 mg group), respectively. The differences between the EPs® 7630 groups and placebo were statistically significant ($p<0.0001$, each), but there was no significant difference between BSS of patients treated with different doses of EPs® 7630 (See Table 5 and Figure 9).

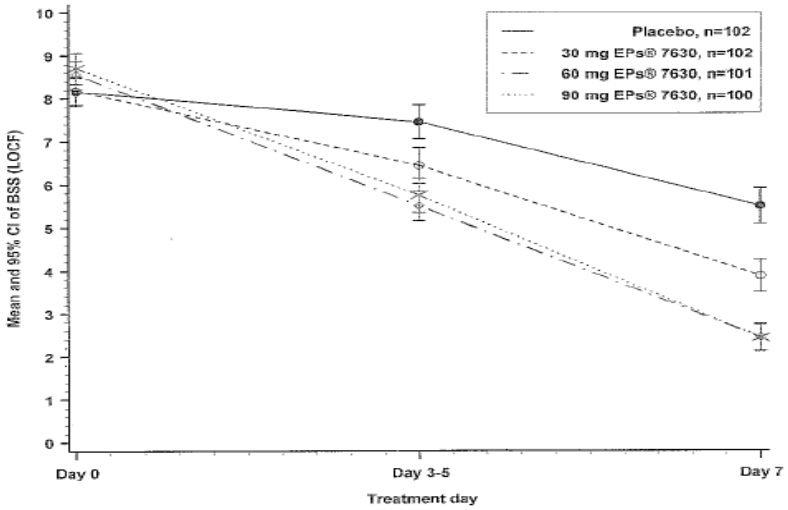


Figure 9: bronchitis-specific symptoms – total score (FAS, LOCF) (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003)

As secondary efficacy parameter the changes of individual symtoms of BSS (Day 0-Day 7) were also analysed (see Table 6).

	FAS (n = 405)			
	Placebo (n = 102)	EPs® 7630 30 mg (n = 102)	EPs® 7630 60 mg (n = 101)	EPs® 7630 90 mg (n = 100)
Coughing	0.7 (0.7) 1.0	1.3 (0.8) 1.0	1.8 (0.8) 2.0	1.7 (0.8) 2.0
Sputum	-0.2 (1.0) 0.0	-0.1 (0.9) 0.0	0.3 (0.9) 0.0	0.3 (0.9) 0.0
Pulmonary rales at auscultation	0.5 (0.7) 0.0	1.0 (0.7) 1.0	1.4 (0.8) 1.0	1.5 (0.8) 2.0
Chest pain while coughing	1.1 (0.8) 1.0	1.4 (0.8) 1.0	1.6 (0.8) 2.0	1.8 (0.8) 2.0
Dyspnoea	0.5 (0.8) 0.0	0.7 (0.7) 1.0	1.0 (0.7) 1.0	1.0 (0.7) 1.0

Table 6: change of individual symptoms of BSS (Day 0-Day 7) (mean (SD), median; LOCF) (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003)

The mean decrease in all individual symptoms of BSS from Day 0 to Day 7 was markedly more pronounced in the EPs® 7630 group than in the placebo group. Pair-wise comparison to placebo showed that the effect of EPs® 7630 on the rate of patients with remission and improvement of symptoms coughing, sputum, pulmonary rales at auscultation, chest pain while coughing and dyspnoea from Day 0 to Day 7 (LOCF: last observation carried forward) was statistically significant for all symptoms ($p<0.0001$, two–sided t-test), except for symtoms sputum ($p=0.2040$) chest pain while coughing ($p=0.0261$) and dyspnoea ($p=0.0405$) in the EPs® 7630 30 mg group.

As secondary efficacy variables, three response criteria were determined: (1) BSS total score less than 3 points on day 7, (2) decrease in BSS total score of at least 7 points from day 0 to day 7, and (3) combination of criteria 1 and 2.

		FAS (n = 405)			
		Placebo (n = 102)	EPs® 7630 30 mg (n = 102)	EPs® 7630 60 mg (n = 101)	EPs® 7630 90 mg (n = 100)
1	BSS total score < 3 at Day 7				
	Patients	6 (5.9%)	25 (24.5%)	58 (57.4%)	55 (55.0%)
	p-value (comparison to placebo)		0.0002	<0.0001	<0.0001
2	Decrease in BSS total score ≥ 7 points from Day 0 to Day 7				
	Patients	7 (6.9%)	15 (14.7%)	44 (43.6%)	46 (46.0%)
	p-value (comparison to placebo)		0.0710	<0.0001	<0.0001
3	Combination of criterion 1 and 2				
	Patients	3 (2.9%)	7 (6.9%)	34 (33.7%)	31 (31.0%)
	p-value (comparison to placebo)		0.1946	<0.0001	<0.0001

Table 7: treatment response (absolute (relative) frequency, two sides p-value chi-squared test; LOCF) (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003)

The number of responders on Day 7 (LOCF) was significantly higher in all EPs® 7630 treatment groups than in the placebo group regarding criterion no.1. Regarding to the second and combined crierterion the advantage to placebo was statistically significant for the EPs® 7630 treatment groups with dosage 60 mg and 90 mg.

The treatment outcome was assessed by both the patient and the investigator using the Integrative Medicine Outcomes Scale (IMOS; a 5-point verbal rating scale describing the general health status of the patient: 1= 'complete recovery', 2= 'major improvement', 3= 'slight-to-moderate improvement', 4= 'no change', 5= 'deterioration').

	FAS (n = 405)			
	Placebo (n = 102)	EPs® 7630 30 mg (n = 102)	EPs® 7630 60 mg (n = 101)	EPs® 7630 90 mg (n = 100)
Investigator's assessment				
Completely recovered	1 (1.0%)	4 (3.9%)	11 (10.9%)	9 (9.0%)
Major improvement	10 (9.8%)	36 (35.3%)	59 (58.4%)	68 (68.0%)
Slight to moderate improvement	48 (47.1%)	54 (52.9%)	28 (27.7%)	22 (22.0%)
No change	35 (34.3%)	8 (7.8%)	3 (3.0%)	1 (1.0%)
Deterioration	8 (7.8%)			
Patient's assessment				
Completely recovered	1 (1.0%)	6 (5.9%)	19 (18.8%)	13 (13.0%)
Major improvement	15 (14.7%)	37 (36.3%)	55 (54.5%)	68 (68.0%)
Slight to moderate improvement	52 (51.0%)	49 (48.0%)	24 (23.8%)	18 (18.0%)
No change	27 (26.5%)	9 (8.8%)	3 (3.0%)	1 (1.0%)
Deterioration	7 (6.9%)	1 (1.0%)		

Table 8: treatment outcome using the Integrative Medicine Outcome Scale (IMOS) on Day 7 (LOCF) (absolute (relative) frequency) (cited from Malek *et al*., 2007c Sudy Report No: 701003.01.003)

All active treatment groups showed a significantly better IMOS (Integrative Medicine Outcome Scale) outcome scale than placebo in the assessment of the investigator (completely recovered 1% vs. 3.9-10.9%, major improvement 9.8% vs. 35.3-68%) and patient (completely recovered 1% vs. 5.9-18.8%, major improvement 14.7% vs. 36.3-68%) (Malek *et al*., 2007c).

Between day 0 and day 7, the number of patients unable to work dropped from 92.2, 87.3, 93.1 and 89% to 52, 21.6, 12.9 and 6% of patients in the placebo, EPs® 7630 30, 60 and 90 mg groups, respectively. This reduction was significantly more pronounced in the active treatment groups than with placebo.

The median duration of inability to work was 8 days for placebo and 6 days for EPs® 7630, i.e. a reduction by 2 days in all active treatment groups ($p<0.0001$, in each case, two-sided U-test) (Matthys *et al.* 2010b).

All documented adverse events were of mild to moderate intensity; their frequency was dose-dependent. The most common adverse effects affected the gastrointestinal system (6/102 (5.9%) patients in the placebo group, 5/102 (4.9%) in the 30 mg group, 9/101 (8.9%) in the 60 mg group and 15/101 (14.9%) in the 90 mg group). No serious adverse events were reported (Matthys *et al.* 2010b). The occurrence of gastrointestinal disturbances increased dose-dependently. Although analyses of the dose–response curve consistently indicate an increasing efficacy of EPs® 7630 tablets with increasing daily doses, but with no additional effect on overall efficacy for a dose above 60 mg daily. The results indicate – taking into account both efficacy and safety – that 60 mg EPs® daily constitutes the optimal dose with respect to the benefit–risk ratio of EPs® 7630 tablets.

According to Schulz (2008) the treatment effect of 3 x 20 mg of EPs® 7630 film-coated tablet is similar to the efficacy of EPs® 7630 solution 3 x 30 drops considering the extent and quickness of the effect.

***Assessor's overall conclusion*:**
Although the difference between the decrease of the BSS score in the placebo 2.7±2.3 and in the two higher doses of EPs 7630® (6.1±2.1 (60 mg group), and 6.3±2.0 points (90 mg group) is statistically significant (p<0.0001, each), its clinical significance is questionable. The patients in this study were suffering only from a moderate grate of disease since the avarege BSS was 8.2, 8.2, 8.6 and 8.7 in the placebo group, in the 30, 60 and 90 mg treatment groups, respectively. Since acute bronchitis is a self-limited condition with great placebo effect at least difference of 4 points (20% of the total symptoms score) between the effect of EPs® 7630 and of placebo is desirable. The actual data are 6.1–2.7= 3.4, 6.3-2.7=3.6 respectively.

The weakness of the efficacy is reflected in the number of patients recovered completely. After 7-day-treatment only 1%, 3.9% 10.9% and 9.0% of the patients recovered completely in the placebo group, in the 30, 60 and 90 mg treatment group, respectively which cannot be considered clinically relevant.

Furthermore there was imbalance between the groups relating to gender distribution and smoking habits at baseline.

4.2.2. Clinical studies (case studies and clinical trials)

Acute bronchitis

Futher three randomised, double-blind, placebo-controlled studies were carried out to evaluate the efficacy and safety of EPs® 7630 (30 drops three times daily) compared to placebo, in adults patients with acute bronchitis.

- UM 26 clinical trial (Neidig *et al*., 2002 clinical trial report; Golovatiouk-Chucalin, 2002; Chuchalin *et al*., 2005; Schulz *et al*., 2007) was performed in 6 centres in Moscow (Russia) from 14 April 2000 to March 2001. 64 patients were treated with EPs® 7630 solution and 60 patients with placebo.
- UM 27 clinical trial (Romberg, 2004c clinical trial report, Matthys *et al*., 2003) was performed in 468 patients (233 patients in the EPs® 7630 solution group and 235 in the placebo group) at 36 study sites (23 in Germany, 13 in Ukraine) from 15 May 2000 to 10 April 2002.
- UM 28 clinical trial (Romberg, 2004a clinical trial report; Matthys and Heger, 2007; Matthys and Funk, 2008) was conducted in 217 patients (108 patients in the EPs® 7630 solution group, 109 patients in the placebo group) at 6 study sites in Moscow from 02 October 2000 to 19 March 2002.

The trials were performed according to a similar design mentioned above. 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 enrollment (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 dyspnoea. Each symptom was assessed by the investigator using a verbal five-point rating scale ranging from zero to four. Based on results of previous studies the average decrease of BSS from baseline was expected to be 5 points under placebo and 7 points under EPs® 7630 with a within-group standard deviation of 3 points. A difference of 1 point was considered clinically relevant in the patient populations in these clinical trials. 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 summarised in Table 9.

For the purpose of comparison the results of the UM 37 dose finding study evaulated in details above (Romberg,2004d UM037 clinical trial report) are also presented again for the EPs® 7630 3 x 30 drops group in Table 9 and Table 11. This dosage is equal with dose applied in the UM 26, UM 27 and UM28 study and the adults patients also suffered from acute bronchitis. The study was performed between 26-Nov-2001 and 09-May-2003 at the 40 investigational sites.

In each study the decrease of BSS was statistically significantly higher in patients treated with EPs® 7630 compared to patients treated with placebo.

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
UM 26 Neidig *et al*., 2002a clinical trial report Chuchalin *et al*., 2005* (also in Golovatiouk and Chuchalin, 2002)	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 124 aged between 18-71 mean age: 36.2 vs.35.9 male: 23.4 vs. 36.7%	64 patients EPs® 7630 30 drops, 3 times daily 60 patients placebo duration: 7 days	1st reduction of BSS on day 7 BSS on day 0: EPs® 7630 9.0±2.2[8] Placebo 9.1±2.2[8]	7.2±3.1 vs. 4.9±2.7 (p<0.0001) *Difference between verum vs. placebo = 7.2-4.9=2.3*
UM 27 Romberg, 2004c Matthys *et al*., 2003# (also in Heger, 2002)	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 468 mean age: 41.1 vs.39.9 male: 40.3 vs. 46.9%	233 patients EPs® 7630 30 drops, 3 times daily 235 patients placebo duration: 7 days	1st reduction of BSS on day 7 BSS on day 0: EPs® 7630 8.4±2.2[8] Placebo 8.0±2.0[8]	5.9±2.9 vs. 3.2±4.1 (p<0.0001) *Difference between verum vs. placebo = 5.9-3.2=2.7*

UM 28 Romberg, 2004a Matthys and Heger, 2007a*, Matthys and Funk, 2008	DB,PC,R, MC	acute bronchitis present (≤48 hours) BSS ≥5 points n= 217 mean age: 37.4 male: 24.4%	108 patients EPs® 7630 30 drops, 3 times daily 109 patients placebo duration: 7 days	1st reduction of BSS on day 7 BSS on day 0: EPs® 7630 8.9±1.6[9] Placebo 8.4±1.8[8]	7.6±2.2 points vs. 5.3±3.2 points (p<0.0001) *Difference between verum vs. placebo) = 7.6-5.3=2.3*
UM 37 Romberg, 2004d **dose-finding study** (see above)	DB,PC,R, MC	acute bronchitis with productive cough present (≤72 hours) BSS ≥8 points n= 637 mean age: 37.7 male: 26.8%	214 patients EPs® 7630 30 drops, 3 times daily 213 patients placebo duration: 7 days (14 days)	1st reduction of BSS on day 7 BSS on day 0: 10.4±1.7[10] for both EPs® 7630 3 x 30 and placebo	7.1±2.8 vs. 7.6±2.5 vs. 0.8±2.8 points *Difference between verum vs. placebo = 7.1-0.8=6.3*

Table 9: Placebo-controlled clinical studies with EPs® 7630 – treatment of acute bronchitis; comparison of the results considering the primary efficacy variable

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

The meta-analysis of these clinical trials made by Agbabiaka *et al*. (2008) also showed a significant decrease of BSS score compared to placebo.

***Assessor's comment*:**

In these studies again the difference of 1 point was considered clinically relevant which cannot be taken as a really clinicaly relevant difference. Although the differences between the decrease of the BSS score in the placebo (4.9±2.7, 3.2±4.1, 5.3±3.2) and in the EPs® 7630 (7.2±3.1, 5.9±2.9, 7.6±2.2) were statistically significant (p<0.0001, each) but not clinically relevant since they did not reach even a 20% of the total symptoms score (20 points) (7.2-4.9= 2.3, 5.9-3.2= 2.7, 7.6-5.3= 2.3), respectively.

The difference was greater, 6.3, in the UM37 dose-finding clinical study (Romberg, 2004d) for the 3 x 30 drops treatment group comparing with placebo. However, this result cannot be considered because the great number of withdrawals (see Table 10). Comparing the data of other studies the reason for the greater number of withdrawals could be that the symptoms of acute bronchitis could be present ≤72 hours still in another study only ≤48 hours. Furhermore the patients in this study were in a little more serious condition (BSS on day 0 10.4±1.7 for both EPs® 7630 3 x 30 and pacebo) than in another studies (UM 26: EPs® 7630 9.0±2.2, placebo 9.1±2.2, UM 27 EPs® 7630 8.4±2.2, placebo 8.0±2.0 and UM 28 EPs® 7630 8.9±1.6, placebo 8.4±1.8) thus the patients in the placebo group in this study could have been more dissatisfied than in other studies and gave up the treatment earlier.

Study	**EPs® 7630**		**Placebo**	
	patient's number/ patient' s number in the group	percent	patient's number/ patient' s number in the group	percent
UM 26 Neidig *et al*., 2002 clinical trial report Chuchalin *et al*., 2005 (also in Golovatiouk and Chuchalin, 2002)	1/64	1.6%	2/60	3.3%
UM 27 Romberg, 2004c; Matthys *et al*., 2003 (also in Heger, 2002)	9/233	3.9%	88/235	37.4%
UM 28 Romberg, 2004a; Matthys and Heger, 2007a; Matthys and Funk, 2008	0/108	0%	10/109	9.2%
UM 37 Romberg, 2004d dose-finding study	6/210	2.8%	177/213	83.1%

Table 10: Number of withdrawals in the clinical studies performed with EPs® 7630 solution in acute bronchitis due to lack of efficacy

According to the authors the clinical relevance of difference in favour of EPs® 7630 is underlined by the results for all evaluable secondary efficacy parameters showing the same tendency.

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
UM 26 Neidig *et al*., 2002 clinical trial report **Chuchalin *et al*.,** 2005* Golovatiouk and Chuchalin, 2002	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 124 mean age: 36.2 vs.35.9 male: 23.4 vs. 36.7%	64 patients EPs® 7630 30 drops, 3 times daily before or after meal 60 patients placebo duration: 7 days	BSS <5 points on day 7 decrease of BSS ≥5 disappearance of individual symptoms on day 7: cough sputum rales/rhonchi chest pain during cough major improvement and recovery rates on day 7 adverse events	95.3% vs. 58.3% (p<0.001) 90.6% vs. 51.7% (p<0.001) 31.3% vs. 5.0% (p<0.0001) 57.8% vs. 28.3% 91.7% vs. 49.2% (p<0.0001) 94.8% vs. 55.8% (p<0.0001) 84.4% vs. 30.0% 23.4% vs.16.7%
UM 27 Romberg, 2004c **Matthys *et al*., 2003**[#] (also in Heger, 2002)	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 468 mean age: 41.1 vs.39.9 male: 40.3 vs. 46.9%	233 patients EPs® 7630 30 drops, 3 times daily before or after meal 235 patients placebo duration: 7 days	BSS<3 points on day 7 decrease of BSS ≥7 disappearance of individual symptoms on day 7: cough sputum chest pain during cough rales/rhonchi dyspnoe working inability on day 7 able to work (days) adverse events ear and labyrinth gastrointestinal	64.4% vs. 37.9%(p<0.0001) 43.3% vs. 23.0% (p<0.0001) similar in the two groups similar in the two groups 83.7% vs. 48.1% (p<0.0001) 77.1.%vs.44.4% p<0.0001) 84.1% vs. 46.7% (p<0.0001) 15.9% vs. 43.0% (p<0.0001) 4.7±3.7 vs.6.3±4.5 (p<0.0001) 8.6% vs. 6.8% 2.2% vs. 0.4% 1.7% vs. 3.0%
UM 28 Romberg, 2004a Matthys and Heger, 2007a* Matthys and Funk, 2008	DB,PC,R, MC	acute bronchitis present (≤48 hours) BSS ≥5 points n= 217 mean age: 37.4 male: 24.4%	108 patients EPs® 7630 30 drops, 3 times daily 109 patients placebo duration: 7 days	BSS <5 points on day 7 decrease of BSS ≥5 BSS<3 points on day 7 decrease of BSS ≥7 complete remission of individual symptoms on day 7: cough sputum rales/rhonchi chest pain during cough dyspnoe complete recovery assessed by the physician satisfaction with treatment (patients) unable towork adverse events	95.4% vs.84.4% 94.4 % vs. 70.6% 85.2% vs. 52.3 % 76.9% vs. 34.9% 51.9% vs. 11.9% 68.3% vs. 40.0% 88.2% vs. 50.0% 93.4% vs. 86.0% 87.9% vs. 76.7% 45.4% vs. 6.4% 84.3% vs. 47.7% 18.45% vs. 33.3% 21.3% vs. 22.0%
UM 37 **Romberg, 2004d**	DB,PC,R, MC	acute bronchitis with productive cough present (≤72 hours) BSS ≥8 points n= 637 mean age: 37.7 male: 26.8%	214 patients EPs® 7630 30 drops, 3 times daily 213 patients placebo duration: 7 days	BSS< 3 points on day 7 complete remission of individual symptoms on day 7 for 3 x 30 vs. placebo: cough symptom sputum rales/rhonchi chest pain during cough dyspnoe recovery rates on Day 7 assessed by the phisician able to work on Day 7	34.1% (3 x 30) vs.5.2% 23.8% vs.1.9% 26.9% vs.3.8% 50.9% vs. 9.0% 61.3% vs. 12.2% 81.4% vs.13.0% 23.4% (3 x 30) vs. 1.9% placebo 78.3% vs. 10.7%

				2nd adverse events(3 x 30 vs. placebo)	9.3% vs. 7.0%

Table 11: Placebo-controlled clinical studies with EPs® 7630 – treatment of acute bronchitis; comparison of the results considering the secondary efficacy variable

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 (4.7±3.7 days vs. 6.3±4.5 days p<0.0001) (Matthys *at al*., 2003). 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 advers events were observed in all trials, but there were no significant differences in the number of advers events reported between two treatment groups (Matthys and Heger, 2007a). Some of advers events reported included gastrointestinal disorders, nervous system disorders (nervousness, fatigue, headache and restlessness), ear and labyrinth disorders (Matthys *et al*., 2003).

Assessor's comment:
Clinicaly relevant difference between EPs® 7630 and placebo should have been presented for the primary outcome criterion.

Open studies

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%. 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 advers events were classified as "gastrointestinal disorders".

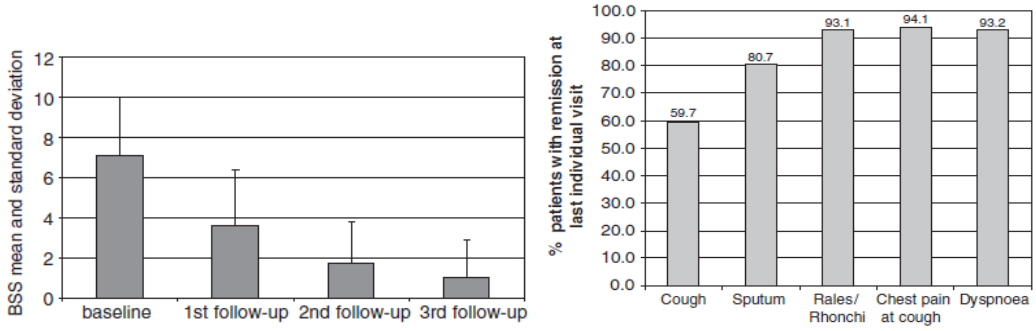


Figure 10: BSS changes during the study period in all patients and remission rates from baseline to last observation for bronchitis-specific symptoms in all patients (Matthys *et al*. 2007)

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 12.). 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 advers events 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).

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% 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 advers events	responder rate 68% ~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 advers events	3.3±3.8 points >70% 66.9-88.2% 78% 18/205

Table 12: Open clinical studies with EPs® 7630 – treatment of acute bronchitis

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 13.). 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 out of 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, randomised, double-blind, placebo-controlled trial. Patients with an age ranging from 18-60 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 visualised 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 the SSS 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-3 x, allergic skin reaction-1x) that occurred in the EPs® 7630 group, the causal relationship with the study drug could not be excluded (Bachert *et al*. 2009).

In a multi-centre, prospective, randomised, placebo-controlled study 272 patients suffering from acute maxillary sinusitis confirmed by radiography were enrolled. Onehundred and thirtysix patients were treated with 3 x 60 drops daily, 136 received placebo for 21 days. Primary outcome criterion was the change of SS (sinusitis-specific symptoms) on day 7. The mean change of SS was -7.0±3.2 in the EPs® 7630 group and 0.0±2.3 points in the placebo group. Beside the significant efficacy, the incidence of adverse events was comparable to placebo in the actively treated group (Romberg, 2004e).

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 randomised 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%) 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).

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 advers events	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 advers events	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%
Romberg, 2004e	DB, MC, R, PC	acute maxillary sinusitis SS ≥12 points n= 272 mean age: 37.7 31.3% male	136 patients EPs® 7630 60 drops, 3 times daily 136 patients placebo duration: 21 days	1st reduction of SS at day 7 2nd advers events	7.0±3.2 vs. 0.0±2.3 points 3.7% vs. 1.5%
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 advers events	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%

Table 13: Clinical studies with EPs® 7630 – treatment of acute sinusitis and common cold.

Abbreviations: DB=double-blind, PC=placebo-controlled, R=randomised, 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 (Kamin *et al*. 2010a; Malek, 2007b Study report 701003.001.002). to identify the appropriate dose of EPs® 7630 and to demonstarte its efficacy, safety and tolerability int he treatment of patients aged 6-18 years suffering from acute bronchitis. The study was performed from February to May 2006 at 16 centres in Ukraine. A total of 399 patients (aged 6–18 years) were randomised 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 evaluation of baseline data revealed no noticeable differences between treatment groups at baseline (see Table 14).

	Placebo n = 101	EPs 7630 (30 mg/day) n = 100	EPs 7630 (60 mg/day) n = 99	EPs 7630 (90 mg/day) n = 99
Gender				
Male	50.5%	53.0%	51.5%	52.5%
Female	49.5%	47.0%	48.5%	47.5%
Age (years)	12.7 ± 3.7	12.5 ± 3.5	12.9 ± 3.7	12.6 ± 3.7
Weight (kg)	47.6 ± 15.1	46.4 ± 13.5	47.1 ± 13.7	47.0 ± 15.3
Height (cm)	155.6 ± 18.5	154.4 ± 17.4	155.7 ± 16.4	154.4 ± 17.3
BMI (kg/m^2)	19.0 ± 2.8	18.9 ± 2.4	19.9 ± 2.6	19.1 ± 3.5
BSS total score: individual symptoms				
Coughing	2.5 ± 0.5	2.5 ± 0.6	2.4 ± 0.6	2.6 ± 0.6
Sputum production	0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.8
Pulmonary rales at auscultation	2.0 ± 0.5	2.0 ± 0.6	1.9 ± 0.5	2.0 ± 0.6
Chest pain while coughing	1.4 ± 0.7	1.4 ± 0.7	1.3 ± 0.7	1.3 ± 0.7
Dyspnoea	0.2 ± 0.5	0.2 ± 0.5	0.3 ± 0.5	0.3 ± 0.5
BSS total score	6.8 ± 1.4	6.9 ± 1.6	6.8 ± 1.5	7.0 ± 1.5
Patients with BSS total score ≥7	53.5%	54.0%	55.6%	59.6%

Table 14: Baseline data (mean±SD or relative frenquencies) (cited from Kamin et al., 2010a)

Assessor's comment:

According to the clinical report Malek et al., 2007b a little more patients were smokers in the placebo group than in the EPs® 7630 30 mg, 60 mg and 90 mg groups: 5/101 (5%), 1/100 (1%) 2/99 (2.0%) and 2/99 (2.0%) patients.

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 (Figure 11).

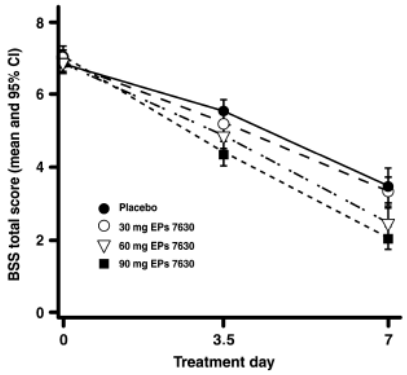


Figure 11: Course of the total score of bronchitis-specific symptoms from Day 0 to Day 7 (cited from Kamin *et al*., 2010a)

There were 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).

Confirmatory analysis

BSS total score (mean (SD), median; LOCF)

		FAS (n = 399)			
		Placebo (n = 101)	EPs® 7630 30 mg (n = 100)	EPs® 7630 60 mg (n = 99)	EPs® 7630 90 mg (n = 99)
Baseline	Day 0	6.8 (1.4) 7.0	6.9 (1.6) 7.0	6.8 (1.5) 7.0	7.0 (1.5) 7.0
	Day 3-5	5.5 (1.8) 5.0	5.2 (1.7) 5.0	4.8 (1.8) 5.0	4.3 (1.7) 5.0
	Day 7 (LOCF)	3.5 (2.5) 3.0	3.3 (2.0) 3.0	2.4 (2.2) 2.0	2.1 (1.6) 2.0
Change	Day 0 – Day 7 (LOCF)	3.3 (2.6) 3.0	3.6 (2.4) 3.5	4.4 (2.4) 5.0	5.0 (1.9) 5.0

Table 15: Results of efficacy analysis (cited from Malek *et al*., 2007b Study report 701003.001.002)

Secondary outcome criteria:

Treatment response (absolute (relative) frequency, two-sided p-value for chi-squared test; (LOCF))

		FAS (n = 399)			
		Placebo (n = 101)	EPs® 7630 30 mg (n = 100)	EPs® 7630 60 mg (n = 99)	EPs® 7630 90 mg (n = 99)
1	BSS total score < 3 at Day 7				
	Patients	43 (42.6%)	36 (36.0%)	57 (57.6%)	72 (72.7%)
	p-value (comparison to placebo)		0.3400	0.0339	<0.0001
2	Decrease in BSS total score ≥ 7 points from Day 0 to Day 7				
	Patients	10 (9.9%)	11 (11.0%)	17 (17.2%)	22 (22.2%)
	p-value (comparison to placebo)		0.7990	0.1325	0.0175
3	Combination of criterion 1 and 2				
	Patients	9 (8.9%)	9 (9.0%)	17 (17.2%)	22 (22.2%)
	p-value (comparison to placebo)		0.9824	0.0824	0.0093

Table 16: Secondary efficacy variables (Cited from Malek *et al*., 2007b Study report 701003.001.002)

The treatment response calculated on the basis of the BSS total scores was higher in the active treatment groups than in the placebo group. 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 (Table 17).

(Day 0 - Day 7) (mean (SD), median; LOCF)

	FAS (n = 399)			
	Placebo (n = 101)	EPs® 7630 30 mg (n = 100)	EPs® 7630 60 mg (n = 99)	EPs® 7630 90 mg (n = 99)
Coughing	1.0 (1.0) 1.0	1.0 (0.9) 1.0	1.3 (0.9) 1.0	1.5 (0.8) 1.0
Sputum	0.0 (0.9) 0.0	0.0 (0.9) 0.0	0.3 (0.8) 0.0	0.3 (0.7) 0.0
Pulmonary rales at auscultation	1.0 (0.9) 1.0	1.1 (0.9) 1.0	1.4 (0.8) 1.0	1.5 (0.8) 2.0
Chest pain while coughing	1.1 (0.8) 1.0	1.2 (0.8) 1.0	1.2 (0.9) 1.0	1.3 (0.7) 1.0
Dyspnoea	0.2 (0.4) 0.0	0.2 (0.5) 0.0	0.2 (0.5) 0.0	0.3 (0.5) 0.0

Table 17: Change in individual symptoms of the BSS total score (cited from Malek *et al*., 2007b Study report 701003.001.002)

The treatment groups with 60 mg and 90 mg doses of EPs® 7630 showed a significantly higher IMOS outcome scale than placebo in the assessment of the investigator (completely recovered 12.9% vs. 21.2-24.2%, major improvement 31.7% vs. 52.5-57.6%) and of patients (completely recovered 14.9% vs. 25.3-28.3%, major improvement 30.7% vs. 48.5-54.5%) (Malek *et al*., 2007b).

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 (Kamin *et al*., 2010a).

Tribanek and Buschule (2008c Study report 701003.01.002) performed a subgroup analysis of the study mentioned above for the patients above 12 years and concluded that the analysis of the total population could also be consistently demonstrated in patients of at least 13 years of age.

Treatment groups were comperable regarding to demographic and anthropometric data. No relevant differences can be seen regarding gender, age, weight, height or BMI.

Bronchitis-specific symptoms – total score
(mean (SD), median, two-sided p-value according to ANCOVA analysis for comparison with the placebo group)

		Patients above 12 years old FAS (n = 227)			
		Placebo (n = 59)	EPs® 7630 30 mg (n = 53)	EPs® 7630 60 mg (n = 59)	EPs® 7630 90 mg (n = 56)
Baseline	Day 0	7.0 (1.4) 7.0	7.0 (1.7) 7.0	6.9 (1.6) 7.0	7.0 (1.5) 7.0
	Day 3-5	5.8 (1.9) 6.0	5.1 (1.9) 5.0	4.8 (1.8) 5.0	4.4 (1.7) 5.0
	Day 7 (LOCF)	4.0 (2.6) 4.0	3.3 (2.1) 3.0	2.5 (2.5) 2.0	2.0 (1.6) 2.0
Change	Day 0 – Day 7 (LOCF)	3.0 (2.6) 3.0	3.7 (2.4) 4.0	4.3 (2.6) 5.0	5.0 (1.9) 5.0
p-value			0.0442	0.0003	< 0.0001

Table 18: Primary efficacy analysis (cited from Tribanek and Buschule, 2008c Study report 701003.01.002)

At baseline, the BSS total score was comperable between the for treatment groups. The score continously decreased in all treatment groups with a definitely quicker and higher reduction in the active treatment groups especially in the 3 x 20 mg and 3 x 30mg active treatment groups (Table 18).

Secondary efficay paramater:

	Patients above 12 years old FAS (n = 227)			
	Placebo (n = 59)	EPs® 7630 30 mg (n = 53)	EPs® 7630 60 mg (n = 59)	EPs® 7630 90 mg (n = 56)
BSS total score < 3 at Day 7	21 (35.6 %)	20 (37.7 %)	34 (57.6 %)	42 (75.0 %)
p-value		0.8142	0.0164	< 0.0001
Decrease in BSS total score ≥ 7 points from Day 0 to Day 7	5 (8.5 %)	5 (9.4 %)	11 (18.6 %)	12 (21.4 %)
p-value		0.8589	0.1067	0.0504
Combination of criterion 1 and 2	5 (8.5 %)	4 (7.6 %)	11 (18.6 %)	12 (21.4 %)
p-value		0.8569	0.1067	0.0504

Table 19: Responders according to the criteria based on the BSS total score (absolute (relative) frequency, p-value: two-sided two sides chi-squared test for comparison with the placebo group; LOCF) (cited from Tribanek and Buschule, 2008c Study report 701003.01.002)

The analysis of the pre-specified response criteria revealed advantages of 3 x 20 mg and 3 x 30 mg EPs 7630 in all three analysed criteria which were not significant due to the small sample size (Table 19).

	Patients above 12 years old FAS (n = 227)			
	Placebo (n = 59)	EPs® 7630 30 mg (n = 53)	EPs® 7630 60 mg (n = 59)	EPs® 7630 90 mg (n = 56)
Investigator's assessment				
Completely recovered	5 (8.5 %)	6 (11.3 %)	10 (17.0 %)	17 (30.4 %)
Major improvement	17 (28.8 %)	20 (37.7 %)	34 (57.6 %)	29 (51.8 %)
Slight to moderate improvement	26 (44.1 %)	18 (34.0 %)	11 (18.6 %)	6 (10.7 %)
No change	7 (11.9 %)	6 (11.3 %)	2 (3.4 %)	3 (5.4 %)
Deterioration	4 (6.8 %)	3 (5.7 %)	2 (3.4 %)	1 (1.8 %)
p-value		0.3620	0.0008	< 0.0001
Patients's assessment				
Completely recovered	6 (10.2 %)	7 (13.2 %)	14 (23.7 %)	18 (32.1 %)
Major improvement	17 (28.8 %)	20 (37.7 %)	30 (50.9 %)	28 (50.0 %)
Slight to moderate improvement	24 (40.7 %)	19 (35.9 %)	10 (17.0 %)	7 (12.5 %)
No change	8 (13.6 %)	4 (7.6 %)	2 (3.4 %)	2 (3.6 %)
Deterioration	4 (6.8 %)	3 (5.7 %)	3 (5.1 %)	1 (1.8 %)
p-value		0.2310	0.0013	< 0.0001

Table 20: treatment outcome using the Integrative Medicine Outcomes Scale (IMOS) on Day 7 (absolute (relative) frequency, two-sided p-value of the Mantel-Haenszel-test for comparison with the placebo group; LOCF) (cited from Tribanek and Buschule, 2008c Study report 701003.01.002)

Low number of patients recovered completely (Table 20).

Assessor's comment:

The dosage in this study is different from that of the product (tablet pharmaceutical form) on the *market. The dosage for the age group of children 6-12 years is 1 tablet, twice a daily (morning, evening). The study was not properly planned, since the different age groups should have been investigated separately. The result of post-analysis is provided only for the age group of 13-18 years. The authors of the subgroup analysis report write the following: „Since the study was not planned to*

demonstrate efficacy in these subgroups of patients the power for showing statistical significance is low (the power of of showing a significant effect with two-sided test at a significance level of 0.05, a treatmenteffect of 1.5 points and a standard deviation of 3.5 points as assumed in the protocol with 50 patients per group is about 56%). Thus, p-values should be interpreted in descriptive way and evaulated with care."

Although the difference between the decrease of the BSS score in the placebo 3.0(2.6) and in the two higher doses of EPs® 7630 (4.3(2.6) 60 mg group), and 5.0 (1.9) points (90 mg group) is statistically significant (p=0.0003 and p<0.0001 respectively) it cannot be considerd clinically significant since it does not reach even a 20% of the total symptoms score (20 points) (4.3-3.0= 1.3, 5.0-3.0=2.0, respectively).

Furthermore, the patients suffered in a mild form of the disease (BSS ≤7) still the proportion of complete recovery was greater only in the group receiving the highest dose compared to the placebo group (5/59 (8.9%) for placebo, 6/53 (11.3%) for EPs® 7630 30 mg, 10/59 (17.0%) for EPs® 7630 60 mg and 17/54 (30.4%) for EPs® 7630 90 mg).

Clinical studies

- **Acute bronchitis**

Blochin *et al*. (1999) (Vornbäumen and Eisebitt, 1998-UM006-Biometrial report) examined the efficacy and tolerability of *Pelargonium* extract **in comparison to acetylcystein for children** with acute bronchitis in a multicentre, randomized, controlled open trial in Moscow (Russia). Sixty children **aged between 5-14 years** (1-1 children less than 6 years in both group and 1 child in acytylcyteine group elder than 12 years) were randomised 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.* Both treatment groups 30/30 patients were treated but the percentage of male was much more lower in the Umckaloabo group than in the acetylcysteine group (33.3% versus 63.3%).

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 (cough, sputum, rales/rhonchi at auscultation, chest pain while coughing and dyspnoea). 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.

At baseline the overall beseline value of BSS was between 5-15 points in both groups with an average of 7±3 (median 6) point for both groups. The most severe symptoms were cough and sputum in both groups but the percentage of patients with at least medium strong of cough was higher in the Umckalaoba group than in acatylcysteine group (63.3% versus 46.7%).

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 (Blochin *et al*. 1999).

Assessor's comment:
The athors did not give information about withdrawals. The two treatment groups were not homogenous in gender distribution and serousness of cough and sputum. The posology is not in line with the product information. 20 drops of liquid preparation every hour up to 12 times on first and on second day of treatment, but no information was given on the true frequency of administration.

In a multicentre (8 sites in Russia), randomised, double-dummy study the efficacy and safety of EPs® 7630 was compared to acetylcysteine in the treatment of children with acute bronchitis between 03 December 1999 and 01 July 2002 (Romberg, 2004b-UM009 Clinical trial report). 104 patients were enrolled in the EPs® 7630 group and 109 in the placebo group. All patients were aged between 6 and 12 and had acute bronchitis with BSS ≥5 points. According to the treatment groups the patients received either EPs® 7630 + placebo matched to acetylcysteine (group I) or acetylcysteine+ placebo matched to EPs® 7630 (group II) over a period of 7 days.

The double-dummy concept of the trial was based on the fact that both placebo applications were matched to EPs® 7630 and acetylcysteine, respectively, with regard to colour, smell, taste and viscosity (EPs® 7630)/consistency (acetylcysteine).

EPs® 7630 and placebo matched to EPs® 7630 were to be administered as 20 drops p.o., 3 times daily, 30 minutes prior to or after meal. Acetylcysteine or placebo matched to Acetylcystein acetylcysteine were to be administered as follows: 200 mg granules of the bag were to be solved in water, juice or cold tea p.o., 2 times daily, prior to the meal.

At baseline the patients in EPs® 7630 group had less frequently reported previous ear, nose and throat (ENT) infections, prevoius treatment of ENT infections, if necessary, and concomitant diseases including respiratory disorders. Previous medication had to be stopped less frequently before start of the trial in the EPs® 7630 group. Patients of the EPs® 7630 group were more frequently living together with their parents, their grandmother and/or grandfather, and they had more frequently a room of their own. Other potentally confounding factors were well balanced between the treatment groups. this suggests, that on avarage the social level was higher inb the EPs® 7630 group than in the Acatylcysteine group. A relevant influence on the efficacy results could not be revealed in the context of the trial.

Ten patients terminated the study earlier, three patients in the EPs® 7630 group and seven from the acetylcysteine group. The most frequently reported reason for premature trial termination/withdrawals was „free of symptoms" for one patients in the EPs® 7630 group and four patients in the acetylcyteine group.

The primary outcome criterion was the change in BSS. At baseline BSS was 7.7±1.9 [7.0]. The two treatment groups did not differ from each other: EPs® 7630: 7.5±1.9 [7.0] points; acetylcysteine: 7.8±2.0 [7.0] points.

After 7 days treatment, the mean change of BSS was -6.7±2.1 in the EPs® 7630 group and -6.6±2.3 in the acetylcysteine group, showing a highly significant non-inferiority of EPs® 7630 compared to acetylcysteine ($p<0.0001$) (Figure 12).

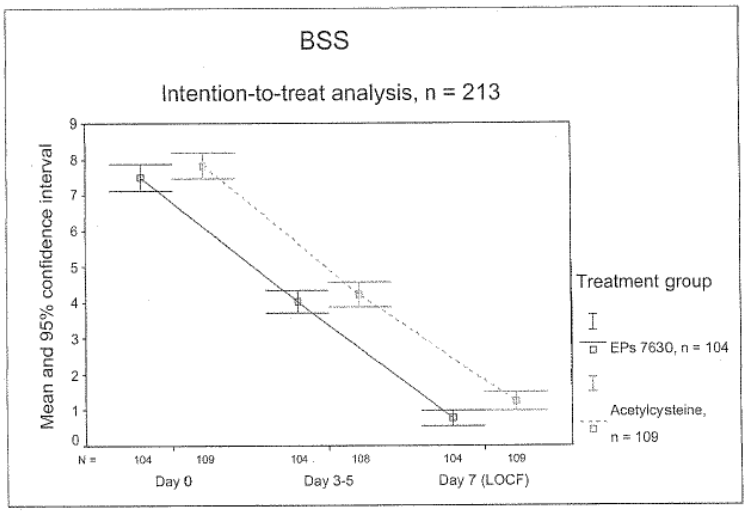


Figure 12: BSS (ITT) (arithmetic means ans corresponding two-sided 95% confidence intervals over time (cited from Romberg, 2004b-UM009 Clinical trial report)

Secondary efficacy variables were the followings:

- prospectively defined response criteria based on BSS
- treatment outcome according to the Integrative Medicine Outcomes Scale (IMOS)
- onset of treatment effect
- consumption of paracetamol
- change of individual symptoms of BSS total score and further symptoms
- health status of the patients using the FGK questionnaire and the questionnaire on health-related quality of life (KINDL-Questionnaire)
- satisfaction with the treatment using Integrative Medicine Patient Satisfaction Scale (IMPSS).

All secondary efficacy parameters showed the same non inferiority of EPs® 7630 compared to acetylcysteine ($p<0.0001$) at the adjusted significance level.

The number of patients experiencing adverse events was lower in the EPs® 7630 group (4.8%) as compared to the acetylcysteine group (9.2%). No serious adverse events were reported (Romberg, 2004b).

Assessor's comment:

This study should have been a three-arm study with a placebo arm besides the EPs® 7630 and acetylcystein group, since the study was double dummy and placebos were available for EPs® 7630 and for acetylcysteine as well. Patients in the EPs® 7630 group took acetylcysteine placebo as well and in acetylcysteine group they received EPs® 7630 placebo as well. The third group could have taken EPs® 7630 placebo and acetylcysteine placebo as well. The two treatment groups were not homogenous in the aspect of previous ear, nose and throat (ENT) infection and of the social circumstances. At baseline the patients in EPs® 7630 group had less frequently reported previous ENT infections, prevoius treatment of ENT infections, if necessary, and concomitant diseases including respiratory disorders. Previous medication had to be stopped less frequently before start of the trial in the EPs® 7630 group. Patients of the EPs® 7630 group were more frequently living together with their parents, their grandmother and/or grandfather, and they had more frequently a room of their own. On average the social level was higher in the EPs®S7630 group than in the acetylcysteine group.

Placebo-controlled trials

Two studies compared EPs® 7630 to placebo in children (1 to 18 years old) with acute bronchitis.

- Study 1 (Malek, 2007a Study No. 701003.01.001, published in Kamin *et al*., 2010b, Schulz, 2008, Matthys and Kamin, 2011,Kamin *et al*., 2012) was performed in 10 centres in Ukraine from 08 February 2006 to 27 April 2006. 103 patients were treated with EPs® 7630 solution and 97 patients with placebo.
- Study 2 (Malek *et al*., 2007d Study No. 701003.01.004, published in Schulz, 2008) was performed in 220 patients (111 patients in the EPs® 7630 solution group and 109 patients in the placebo group) at 11 study sites Moscow (Russia) from 22 March 2006 to 25 May 2006.

In both clinical studies patients, 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 before meals with some fluid. The primary efficacy parameter was the change in the total score of the five bronchitis specific symptoms (BSS) – coughing, sputum, pulmonary rales at auscultation, chest pain while coughing and dyspnoea - assessed by the physicians by the use of a five point verbal rating test. The statistical method was the same: adaptive group-sequential design with interim analysis. All statistics in the clinical reports were given using last observation carried forward (LOCF) unless otherwise stated.

Witdrawals

Study 1: Three patients in the placebo group terminated the study prematurely after radomisation two of them due to lack of efficacy and one patient due to adverse event (acute pneumonia) that was assessed as not realted to the study medicarion. Major protocol deviations were assessed in 7 patients each in the EPs® 7630 and placebo group. Thus the protocol analysis set (PPS) comprised 186 patients, 96 patients in the EPs® 7630 and 91 patients in the placebo group.

Study 2: Two patients in the placebo group and 1 patient in the EPs® 7630 were withdrawn the study because of lack of efficacy. Alltogether 13 patients in the EPs® 7630 and 17 patients were excluded from the PPS due to protocol violations leading to 98 patients in the EPs 7630 and 92 patients in placebo group.

Baseline characteristics

Study 1: Statistically significant baseline difference were observed regarding to bronchitis specific symptom „chest pain while coughing" (see Table 21) and the general symptom „absence of appetite. All other baseline parameters showed no baseline difference berween the two treatment groups.

	FAS (n = 200)		
	EPs® 7630 (n = 103)	Placebo (n = 97)	p-value
Bronchitis-specific symptoms total score	4.8 (1.3) 5.0	4.7 (1.1) 5.0	0.3970
Individual bronchitis-specific symptoms:			
Coughing	2.5 (0.6) 2.0	2.4 (0.6) 2.0	0.1431
Sputum*	0.7 (0.7) 1.0 (n = 68)	0.8 (0.8) 1.0 (n = 62)	0.3991
Pulmonary rale at auscultation	2.0 (0.6) 2.0	1.9 (0.5) 2.0	0.5667
Chest pain while coughing*	1.6 (0.6) 2.0 (n = 68)	1.3 (0.7) 1.0 (n = 62)	0.0121
Dyspnoea	0.4 (0.6) 0.0	0.4 (0.6) 0.0	0.7909

* These items could only be analyzed for patients more than 6 years old and are not part of the BSS total score for confirmatory analysis

	PPS (n = 186)		
	EPs® 7630 (n = 96)	Placebo (n = 90)	p-value
Bronchitis-specific symptoms total score	4.8 (1.3) 5.0	4.7 (1.1) 5.0	0.3874
Individual bronchitis-specific symptoms:			
Coughing	2.5 (0.6) 2.0	2.4 (0.6) 2.0	0.1632
Sputum*	0.7 (0.7) 1.0 (n = 68)	0.8 (0.8) 1.0 (n = 61)	0.4852
Pulmonary rales at auscultation	2.0 (0.6) 2.0	1.9 (0.5) 2.0	0.5567
Chest pain while coughing*	1.6 (0.6) 2.0 (n = 68)	1.3 (0.7) 1.0 (n = 61)	0.0143
Dyspnoea	0.4 (0.6) 0.0	0.4 (0.6) 0.0	0.8878

* These items could only be analyzed for patients more than 6 years old and are not part of the BSS total score for confirmatory analysis
Source: Appendix 16.2.II.6.2.2, Table 1.1 and Tables 6.1.1.3 to 6.1.5.3 and Appendix 16.2.III.1.2, Table 2

Table 21: Outcome measure at baseline (Day 0) (maean (SD), median, p-values according to two-sided t-test) (cited from Malek, 2007a Study No. 701003.01.001)

Study 2: Baseline parameters, including BSS total score, showed no difference between both treatments groups (see Table 22).

	FAS (n = 220)		
	EPs® 7630 (n = 111)	Placebo (n = 109)	p-value
Bronchitis-specific symptoms (BSS, total score)	6.0 (1.6) 6.0	5.8 (1.3) 6.0	0.4776
Individual bronchitis-specific symptoms:			
Coughing	2.8 (0.6) 3.0	2.8 (0.6) 3.0	0.7742
Sputum*	0.9 (0.8) 1.0 (n=71)	0.8 (0.8) 1.0 (n=70)	0.2550
Pulmonary rales at auscultation	2.3 (0.8) 2.0	2.2 (0.6) 2.0	0.5997
Chest pain while coughing*	1.3 (0.9) 1.0 (n=72)	1.3 (0.8) 1.0 (n=70)	0.7253
Dyspnoea	0.9 (0.9) 1.0	0.8 (0.8) 1.0	0.3183

* These items could only be analyzed for patients more than 6 years old and are not part of the BSS total score

	PPS (n = 190)		
	EPs® 7630 (n = 98)	Placebo (n = 92)	p-value
Bronchitis-specific symptoms (BSS, total score)	6.0 (1.6) 6.0	5.8 (1.3) 6.0	0.5067
Individual bronchitis-specific symptoms:			
Coughing	2.8 (0.6) 3.0	2.8 (0.6) 3.0	0.9212
Sputum*	1.0 (0.8) 1.0 (n=66)	0.8 (0.8) 1.0 (n=63)	0.3206
Pulmonary rales at auscultation	2.3 (0.8) 2.0	2.2 (0.7) 2.0	0.4638
Chest pain while coughing*	1.3 (0.9) 1.0 (n=67)	1.2 (0.8) 1.0 (n=63)	0.8398
Dyspnoea	0.9 (0.9) 1.0	0.8 (0.8) 1.0	0.5403

* These Items could only be analyzed for patients more than 6 years old and are not part of the BSS total score

Table 22: Outcome measure at baseline (Day 0) (maean (SD), median, p-values according to two-sided t-test) (cited from Malek *et al*., 2007d Study No. 701003.01.004)

Efficacy

The primary outcome measure was the change in the adapted total score of bronchitis-specific symptoms (BSS) from Day 0 to Day 7. According to Ammendment No.1, dated 28 July 2006 and No.2 dated 31 August 2005 the definition of response criteria was adopted to the inability of patients between 1 and 6 years of age to provide adequate information about the BBS items „sputum" and „Chest pain while coughing". Therefore these items were omitted from the evaluation of the BSS total score in the total population. Thus, the BBS considered for comfirmatory analysis in the total population comprised for „coughing", „pulmonary rales at ausculation" and „dyspnoea". This lead to a maximal score of 20 instead of 12 possible points.

***Assessor's comment**:*

Unfortunately the difference between the BSS used in this study and BSS used in other studies (three items versus five items) is not emphasized properly. The number of items of BSS is not mentioned at the begining of the clinical report (Malek, 2007a) only later. It can not be found in the abstract of the article writen by Kamin et al. 2011 and in the article written by Schulz (2008). The BSS which contains five elements is validated only.

The primary outcome measure was the change in the total score of bronchitis specific symptoms (BSS) from Day 0 to Day 7. The BSS considered for the total score in the total population were „Coughing", Pulmonary rales at asculation" and „Dyspnoea".

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 ($p<0.0001$).

Subgroup analysis were performed for patients older than 6 years of age for the BBS total score with all 5 items including „sputum" and „chest pain while coughing" as well. In this case the maximal score can be 20 points.

Study	Design	Study population	Treatment	Endpoints	Results (EPs® 7630 vs. placebo)
Study 1 (Malek, 2007a) Kamin *et al.*, 2010b Schulz, 2008b	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 200 aged between 1-18 mean age: 9.4 (5) vs. 9.5 (5.1) male: 48.5 % vs. 46.4%	103 patients EPs® 7630 97 patients placebo patentients from 1 to 6 years: 10 drops verum or placebo 3 times daily patients <6 to 12 years: 20 drops verum or placebo 3 times daily patients >12 to 18 years: 30 drops, 3 times daily duration: 7 days	for the total population reduction of BSS on day 7 (BSS on day 0: EPs® 7630 = 4.8 ±1.3[5.0] placebo = 4.7 ± 1.1[5.0]) total score maximum=12 for patients >6 years only reduction of BSS on day 7 (BSS on day 0: EPs7630 7.2 ±1.9[7.0] placebo 6.7 ± 1.3[7.0]) total score maximum=20	for the total population 3.4±1.8 vs. 1.2±1.8 (p<0.0001) *Difference between verum vs. placebo = 3.4-1.2=2.2* for patients >6 years only 5.2±2.5 vs. 2.0±2.5 (p<0.0001) *Difference between verum vs. placebo = 5.2-2.0=3.2*
Study 2 (Malek *et al.*, 2007d) (Schulz, 2008b)	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 220 mean age: 8.7 vs.9.2 male: 48.6% vs. 50.5%	111 patients EPs® 7630 109 patients placebo patentients from 1 to 6 years: 10 drops verum or placebo 3 times daily patients <6 to 12 years: 20 drops verum or placebo 3 times daily patients >12 to 18 years: 30 drops, 3 times daily 97 patients placebo duration: 7 days	for total population: reduction of BSS on day 7 (BSS on day 0: EPs® 7630 = 6.0±1.6[6.0] placebo = 5.8±1.3[6.0]) total score maximum=12 for patients >6 years only reduction of BSS on day 7 (BSS on day 0: EPs® 7630 = 8.0±2.4[8.0] Placebo = 7.7±1.8[7.0]) total score maximum=20	for the total population: 4.4±1.6 vs. 2.9±1.4 (p<0.0001) *Difference between verum vs. placebo = 4.4-2.9= 1.5* for patients >6 years only 6.1±2.3 vs. 3.8±23 (p<0.0001) *Difference between verum vs. placebo= 6.1-3.8=2.3*

Table 23: Placebo-controlled clinical studies with EPs® 7630 – treatment of acute bronchitis; comparison of the results considering the primary outcome criteria

Difference between centres:

Study 1: Except for the placebo group in centes No.8 and 10 all centres showed decrease in BBS total score from Day 0 to Day 7 in both treatment group (0.0 and -0.5 respectively). A statistically significant stronger effect EPs® 7630 on the decrease in BBS total score could be observed for FAS far all centres, except Centres No.1 and 4. (0.0 and 0.5 respectively). The treatment group differences were especially pronounced in Centres No. 6, 8 and 10 (4.4, 4.1 and 4.8 respectivelly). No conspicuous findings were identified for these or any other center.

Study 2: All centres showed a decrease in BSS total score from Day 0 to Day 7 in both treatment groups. In all centres the mean decrease in BSS total score from Day 0 to Day 7 was more pronounced in the EPs® 7630 group than the placebo group.

Secondary outcomes

Secondary efficacy variables were the same as mentioned above except the response criteria based on the score of bronchitis–specific symptoms since the maximal score was only 12.

For total population: A: BSS<3 points on day 7, B: Decrease of BSS ≥ 4, A+B.

For patient older 6 years of age A: BSS<3 points on day 7; B: Decrease of BSS ≥ 7, A+B

Study	Design	Study population	Treatment	Endpoints	Results EPs® 7630 vs. placebo (n= number of patients)
Study 1 (Malek, 2007a) **Kamin *et al.*, (2010b) Schulz, 2008b**	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 200 aged between 1-18 mean age: 9.4 (5) vs. 9.5 85.1) mmmale: 48.5 % vs. 46.4%	103 patients EPs® 7630 97 patients placebo patentients from 1 to 6 years: 10 drops verum or placebo 3 times daily patients <6 to 12 years: 20 drops verum or placebo 3 times daily patients >12 to 18 years: 30 drops, 3 times daily duration: 7 days	For the total population A: BSS <3 points on day 7 B: decrease of BSS ≥ 4 A+B *Total score maximum=12!* For patients >6 years only A: BSS <3 points on day 7 B: decrease of BSS ≥ 7 A+B: *Total score maximum=20!* change in the individual symptoms of BSS on day 7: cough* Remission sputum*# remission rales/rhonchi remission chest pain during cough*# remission dyspnoea* treatment outcome (IMOS) complete recovery rates on day 7 (investigator's opinion) complete recovery rates on day 7 (patients's opinion) adverse events	83.5% vs. 32.0% (p<0.001) 45.6% vs. 13.4% (p<0.001) 45.6% vs. 13.4% (p<0.001) 64.7% vs. 16.1% (p<0.001) 30.9% vs. 3.2% (p<0.001) 26.5% vs. 3.2% p= 0.0002 1.5±0.9 vs. 0.5±0.9 (p<0.0001) 20(19.4%) vs. 2 (2.1%) (n=103 n=97) 0.1±0.8 vs.-0.1±0.0 (p= 0.0723) (n=68 n=62) 12 (34.3%) vs. 3 (8.6%) (n=35 n=35) 1.5±0.8 vs. 0.6±1.0 (p<0.0001) 61(59.2%) vs.17 (17.5%) (n=103 n=97) 1.5±0.6 vs. 0.7±0.8 (p<0.0001) (n=68 n=62) 89 (96.7%) 37 (48.1%) (n=92 n=77) 0.4±0.6 vs. 0.2±0.6 (p=0.0466) (n=32 n=33) 22 (21.4%) vs. 2 (2.1%) (p<0.0001) 24 (23.3%) vs. 4 (4.1%) (p<0.0001) 30.1% vs.24.7%
Study 2 (Malek *et al.*, 2007d) Schulz, 2008b	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points n= 220 mean age: 8.7 vs.9.2 48.6 % vs. 50.5% male	111 patients EPs® 7630 109 patients placebo patentients from 1 to 6 years: 10 drops verum or placebo 3 times daily patients <6 to 12 years: 20 drops verum or placebo 3 times daily patients >12 to 18 years: 30 drops, 3 times daily 97 patients placebo duration: 7 days	For the total population A: BSS <3 points on day 7 B: decrease of BSS ≥4 A+B For patients >6 years only A: BSS <3 points on day 7 B: decrease of BSS ≥ 7 A+B change in the individual symptoms of BSS on day 7: cough* remission sputum*# remission pulmonary rales* remission chest pain during cough*# remission dyspnoea* remission Treatment outcome (IMOS) complete recovery rates on	81.1% vs. 37.6%(p<0.0001) 73.9% vs. 36.7% (p<0.0001) 64.9% vs. 24.8% (p<0.0001) 72.2% vs. 27.1%(p<0.001) 34.7% vs. 11.4% p=0.0009 25.5% vs. 10.0% p=0.0170 n=72 n=70 1.8±0.8 vs. 1.2±0.8 (p<0.0001) 24 (21.6.4%) vs. 5 (4.6%) (n=111 n=109) 0.7±1.0 vs. 0.1±0.9 (p<0.0001) (n=71 n=70) 31 (67.4%) vs. 13 (33.3%) (n=46 n=39) 1.8±0.9 vs. 1.0±0.9 (p<0.0001) 72(65.5%) vs.23 (21.1%) (n=110 n=109) 1.2±1.0 vs. 2.0±07 (p=0.2548) (n=72 n=70) 53 (91.4%) vs. 41 (69.5%) (n=58 n=59) 0.8±1.0 vs. 0.7±1.0 (p=0.3252) 63 (90.0%) vs. 56 (90.3%)

				day 7 (investigator's opinion) complete recovery rates on day 7 (patients's opinion) adverse events	(n=70 n=62) 53 (47.7%) vs. 12 (11.0%) (p<0.0001) 50(45.0%) vs. 12(11.0%) (p<0.0001) 2 cases vs. 1 case

Table 24: Placebo-controlled clinical studies with EPs® 7630 – treatment of acute bronchitis; comparison of the results considering the secondary efficacy variable

*Number of patients with symptom on Day 0, calculation of rates are based on these baseline numbers, #These items could only be analyzed for patients more than 6 years old and are not part of the BSS total score for confirmatory, remission: Symptom mild, moderate, severe or very severe on Day 0 and not present on Day 7 (IMOS_Integrative Medicine Outcome Scale)

Significant differences were found in the individual symptoms 'coughing' (in study 1: 1.5±0.9 vs. 0.5±0.9; in study 2: 1.8±0.8 vs. 1.2±0.8) and 'pulmonary rales at auscultation' (in study 1: 1.5±0.8 vs. 0.6±1.0; in study 2: 1.8±0.9 vs. 1.0±0.9) in favour of the EPs® 7630group (both with p-values <0.0001, two-sided t-test). The item 'dyspnea' showed a non-significant advantage for EPs7630 (see Table 24) The assessment of general symptoms showed pronounced improvement in the active treatment group and was significant for the items absence of appetite and headache (p<0.0001 and p=0.0003, respectively, two-sided t-test). The onset of treatment effect occurred significantly earlier in the EPs® 7630 group as compared to placebo (p<0.0001, two-sided Mantel-Haenszel χ2-test). The results of the evaluation of treatment outcome (IMOS) by the investigator at day 7 showed a significantly better IMOS outcome for patients treated with EPs® 7630 than placebo (p<0.0001, two-sided Mantel-Haenszel χ2-test). Patients' IMOS assessments showed a very strong agreement with the assessments made by the investigators (Malek *et al.*, 2007a and 2007d). In the EPs® 7630 group, the number of patients keeping bed rest dropped from 42.7% (44/103) at baseline to 1.9% (2/103) patients on day 7 compared with a decrease from 42.3% (41/97) to 18.6% (18/97) for patients in the placebo group. Correspondingly, the number of patients able to attend kindergarten, school or work on day 7 increased more markedly in the EPs® 7630 group than in the placebo group (50/103 patients (48.5%) of the EPs® 7630 group and 12/97 patients (12.4%) of the placebo group (Malek *et al*., 2007a).

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 out of 220 patients reported adverse events during the trial (Schulz, 2008b).

Post analyses

The post analyses of Study 1 and Study 2 was performed to comfirm the positive effects of EPs® 7630 in patients below 7, between 7-12 and above 12 years (Tribanek and Buschulte, 2008a; Tribanek and Buschulte, 2008b). In both studies the definition of the response criteria was changed. In the case of patients group below 7 the BSS has only three itmes: cough, pulmonary rales at asculation, dyspnoe. Thus maximum reachable BSS total score was 12 points. In the subgroup analysis of patients above 6 years old the BSS total score additionaly comprised the symtoms sputum and pulmonary rales at ausculation, heightening the maximum score to 20 points. Due to lower number of items composing the BBS totsal score, the subgroup of children below 7 years old showed smaller BSS total scores compared to other children.

Post- analysis of study 1 (Tribanek and Buschulte, 2008a Study report 70103.01.001)

The subsets of patients in the three subgroups were comparable between the treatment groups regarding demographic and anthropometric data. No relevant differences can be seen regarding gender, age, weight, height or BMI within the groups.

Primary efficacy

Patients less than 7 years old FAS (n = 70)			
	EPs® 7630 (n = 35)	Placebo (n = 35)	p-value
Day 0	4.7 (0.8) 5.0	4.7 (1.0) 5.0	
Day 3-5	3.2 (0.9) 3.0	4.4 (1.2) 4.0	
Day 7 (LOCF)	1.6 (1.1) 3.0	3.8 (1.9) 4.0	
Day 0 – Day 7 (LOCF)	3.1 (1.5) 3.0	0.9 (1.9) 1.0	< 0.0001
Patients between 7 and 12 years old FAS (n = 62)			
	EPs® 7630 (n = 33)	Placebo (n = 29)	p-value
Day 0	7.4 (1.9) 7.0	6.7 (1.3) 7.0	
Day 3-5	4.4 (1.8) 5.0	5.8 (1.4) 6.0	
Day 7 (LOCF)	1.8 (1.8) 1.0	4.5 (2.5) 4.0	
Day 0 – Day 7 (LOCF)	5.6 (2.8) 6.0	2.3 (2.7) 3.0	< 0.0001
Patients above 12 years old FAS (n = 68)			
	EPs® 7630 (n = 35)	Placebo (n = 33)	p-value
Day 0	7.0 (1.9) 7.0	6.8 (1.3) 7.0	
Day 3-5	4.3 (1.5) 4.0	5.6 (1.2) 6.0	
Day 7 (LOCF)	2.0 (1.3) 2.0	5.0 (2.1) 5.0	
Day 0 – Day 7 (LOCF)	4.9 (2.0) 5.0	1.8 (2.3) 2.0	< 0.0001

Table 25: Bronchitis-specific symptoms- total score (mean (SD), median, one-sided p-value according to ANOVA analysis)(cited from Tribanek and Buschulte, 2008a Study report 70103.01.001)

At baseline the BSS total score was comperabel between the two groups within the subgroups, whereas for subgroup of patients between 7-12 years somewhat lower scores were observed in the placebo group. The BSS total score contiously decreased and a statistically significant superiority of EPs 7630 regarding the difference in change of BSS total score between Day 0and Day 7 was shown in both treatments groups of all three subgroups (Table 25).

Post-analysis of study 2 (Tribanek and Buschulte, 2008b Study report 70103.01.004)

The subsets of patients in the three subgroups aged below 7 years and between 7 and 12 years were comparable between the treatment groups regarding demographic and anthropometric data. No relevant differences can be seen regarding gender, age, weight, height or BMI within the groups. The proportion of male and female patients were somewhat shifted towards male patients in the placebo group of patients below 7 years old. The patients treated with placebo in the subgroup of patients above 12 years old were almost one year older and thus were larger and outweighted the patients in the EPs® 7630 group (Table 26).

(Sex: absolute (relative) frequency and two-sided χ^2- test p-value; age, weight, height and BMI: mean (SD), median and two-sided Wilcoxon-test p-value)

Patients less than 7 years old FAS (n = 78)			
	EPs® 7630 (n = 39)	**Placebo (n = 39)**	**p-value**
Sex			
male	18 (46.2%)	25 (64.1%)	0.1110
female	21 (53.8%)	14 (35.9%)	
Age [years]	3.5 (1.5) 3.0	3.6 (1.8) 4.0	0.7762
Weight [kg]	16.3 (3.5) 15.0	16.7 (4.2) 17.0	0.6995
Height [cm]	102.0 (13.1) 102.0	102.0 (14.6) 104.0	0.8572
BMI [kg/m^2]	15.6 (1.5) 15.7	15.9 (1.5) 15.9	0.5689
Patients between 7 and 12 years old FAS (n = 72)			
	EPs® 7630 (n = 37)	**Placebo (n = 35)**	**p-value**
Sex			0.4868
male	21 (56.8%)	17 (48.6%)	
female	16 (43.2%)	18 (51.4%)	
Age [years]	8.7 (1.8) 8.0	9.1 (2.0) 9.0	0.3640
Weight [kg]	30.7 (9.5) 27.0	30.8 (7.1) 29.0	0.4596
Height [cm]	132.9 (11.6) 128.0	135.7 (12.3) 131.0	0.2317
BMI [kg/m^2]	16.9 (2.6) 16.3	16.5 (1.8) 16.5	0.4213
Patients above 12 years old FAS (n = 70)			
	EPs® 7630 (n = 35)	**Placebo (n = 35)**	**p-value**
Sex			0.6256
male	15 (42.9%)	13 (37.1%)	
female	20 (57.1%)	22 (62.9%)	
Age [years]	14.6 (1.4) 14.0	15.4 (1.4) 15.0	0.0078
Weight [kg]	51.7 (9.1) 52.0	56.5 (9.9) 56.0	0.0068
Height [cm]	161.6 (7.9) 162.0	164.5 (8.4) 164.0	0.0644
BMI [kg/m^2]	19.6 (2.1) 19.7	20.7 (2.1) 20.6	0.0112

Table 26: Demographic and antropometric data (cited from Tribanek and Buschulte, 2008b Study report 70103.01.004

Primary efficacy

Patients less than 7 years old FAS (n = 78)			
	EPs® 7630 (n = 39)	Placebo (n = 39)	p-value
Day 0	6.3 (1.3) 6.0	6.3 (1.1) 6.0	
Day 3-5	3.5 (1.4) 4.0	4.7 (1.3) 5.0	
Day 7 (LOCF)	1.6 (1.5) 1.0	3.0 (1.5) 3.0	
Day 0 – Day 7 (LOCF)	4.6 (1.8) 5.0	3.3 (1.3) 3.0	0.0001
Patients between 7 and 12 years old FAS (n = 72)			
	EPs® 7630 (n = 37)	Placebo (n = 35)	p-value
Day 0	7.9 (2.2) 7.7	7.1 (1.4) 7.0	
Day 3-5	5.1 (2.2) 5.0	5.3 (1.6) 5.0	
Day 7 (LOCF)	2.0 (1.8) 2.0	3.5 (2.0) 3.0	
Day 0 – Day 7 (LOCF)	6.0 (2.1) 6.0	3.5 (2.4) 4.0	< 0.0001
Patients above 12 years old FAS (n = 70)			
	EPs® 7630 (n = 35)	Placebo (n = 35)	p-value
Day 0	8.1 (2.6) 8.0	8.3 (1.9) 8.0	
Day 3-5	4.8 (1.5) 5.0	6.4 (2.0) 6.0	
Day 7 (LOCF)	1.8 (1.7) 1.0	4.3 (2.2) 4.0	
Day 0 – Day 7 (LOCF)	6.3 (2.5) 6.0	4.0 (2.2) 4.0	< 0.0001

Table 27: Bronchitis-specific symptoms- total score (mean (SD), median, one-sided p-value according to ANOVA analysis) (cited from Tribanek and Buschulte, 2008b Study report 70103.01.004)

At baseline the BBS total score was comparable between the two treatment groups, whereas for the subgroup of patients between 7 and 12 years somewhat lower scores were observed in the placebo group. Due to lower number of items composing the BSS total score, the subgroup of children below 7 years old showed smaller total scores compared to the older children. The BSS total score contiously decreased and a statistically significant superiority of EPs 7630 regarding the difference in change of BSS total score between Day 0and Day 7 was shown in both treatments groups of all three subgroups (Table 27).

Study	Design	Study population	Treatment	BSS on Day 0 (EPs® 7630 vs. placebo)	Decrease in BSS in points (EPs® 7630 vs. placebo)
Study 1 (Malek, 2007a) Tribanek and Buschulte, 2008a Study report 70103.01.001	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points 70 patients from 1 to 6 years EPs® 7630:35 placebo: 35	patients from 1 to 6 years: 10 drops verum or placebo 3 times daily	for patients less than 7 4.7±0.8[5.0] vs.4.7±1.0[5.0] Total score maximum=12!	for the patients less than 7 3.1±1.5 vs. 0.9±1.9 (p<0.0001) *Difference between verum vs. placebo = 3.1–0.9=2.2*
		62 patients between 7 and 12 years EPs® 7630:33 placebo: 29	patients <6 to 12 years: 20 drops verum or placebo 3 times daily	for patients <6 to 12 7.4 ±1.9[7.0] vs. 6.7±1.3[7.0] Total score maximum=20	for patients >6 to 12 5.6±2.8 vs. 2.3±2.7 (p<0.0001) *Difference between verum vs. placebo = 5.6-2.3=3.3*
		68 patients above 12 years EPs 7630:35 placebo: 33	patients >12 to 18 years: 30 drops, 3 times daily duration: 7 days	For patients above 12 7.0±1.9[7.0] vs. 6.8±1.3[7.0] Total score maximum=20	for patients above 12 4.9±2.0 vs. 1.8±2.3 (p<0.0001) *Difference between verum vs. placebo = 4.9-1.8=3.1*
Study 2 (Malek et al., 2007d) (Schulz, 2008b) Tribanek and Buschulte, 2008b Study report 70103.01.004	DB,PC,R	acute bronchitis present (≤48 hours) BSS ≥5 points 78 patients from 1 to 6 years EPs® 7630: 39 placebo: 39	patients from 1 to 6 years: 10 drops verum or placebo 3 times daily	for patients less than 7 6.3±1.3[6.0] vs. 6.3±1.1[6.0] Total score maximum=12!	for the total population: 4.6±1.8 vs. 3.3±1.3 (p<0.0001) *Difference between verum vs. placebo = 4.6-3.3=1.3*
		72 patients between	patients <6 to 12	for patients <6 to 12	for patients >6 to 12

		7 and 12 years EPs® 7630: 33 placebo: 29 70 patients above 12 years EPs® 7630: 35 placebo: 35	years: 20 drops verum or placebo 3 times daily patients >12 to 18 years: 30 drops, 3 times daily duration: 7 days	7.9±2.2[7.7] vs. 7.1±1.4[7.0] Total score maximum=20 for patients above 12 7.0±1.9[7.0] vs. 6.8±1.3[7.0] Total score maximum=20	6.0±2.1 vs. 3.5±2.4 (p<0.0001) *Difference between verum vs. placebo = 6.0-3.5=2.5* for patients above 12 6.3±2.5 vs. 4.0±2.2 (p<0.0001) *Difference between verum vs. placebo = 6.3-4.0=2.3*

Table 28: Placebo-controlled clinical studies with EPs® 7630 – treatment of acute bronchitis. Comparison of the results considering the primary efficacy variable.

Assessor's comment:

Although the differences between the decrease of the BSS score comparing the EPs® 7630 with placebo were statistically significant for each age groups (p<0.0001, each), they were not clinically relevant since they did not reach even a 20% of the total symptoms score.

In the case of total 12 points of BSS 2.4 points of difference can be considered clinically relevant. The difference between the two treatment groups is only 3.1 – 0.9 = 2.2 in study 1; 4.6 - 3.3 = 1.3 in study 2 for the age group below 7 years of age.

In the case of total 20 points of BSS 4.0 points of difference can be considered clinically relevant. The difference between the two treatment groups is only 5.6 - 2.3 = 3.3 in study 1; 6.0 - 3.5 = 2.5 in study 2 for the age group between 7-12 years of age. For the age group above 12 years of age the difference is 4.9 - 1.8 = 3.1 in study 1; 6.3 - 4.0 = 2.3 in study 2 (Table 28).

Secondary parameters:

Study 1:

Patients less than 7 years old FAS (n = 70)			
	EPs® 7630 (n = 35)	**Placebo (n = 35)**	**p-value**
Coughing	1.4 (0.8) 1.0	0.1 (0.9) 0.0	< 0.0001
Pulmonary rales at auscultation	1.4 (0.9) 1.0	0.0 (0.9) 0.0	< 0.0001
Dyspnoea	0.3 (0.5) 0.0	0.2 (0.7) 0.0	0.3122
Patients between 7 and 12 years old FAS (n = 62)			
	EPs® 7630 (n = 33)	**Placebo (n = 29)**	**p-value**
Coughing	1.7 (1.0) 2.0	0.6 (1.0) 0.0	< 0.0001
Sputum	0.2 (0.9) 0.0	- 0.1 (0.8) 0.0	0.3270
Pulmonary rales at auscultation	1.7 (0.8) 2.0	0.8 (1.0) 1.0	0.0002
Chest pain while coughing	1.6 (0.6) 2.0	0.7 (0.9) 1.0	< 0.0001
Dyspnoea	0.4 (0.7) 0.0	0.2 (0.6) 0.0	0.2560
Patients above 12 years old FAS (n = 68)			
	EPs® 7630 (n = 35)	**Placebo (n = 33)**	**p-value**
Coughing	1.5 (0.8) 2.0	0.5 (0.8) 0.0	< 0.0001
Sputum	0.1 (0.7) 0.0	- 0.2 (0.7) 0.0	0.1077
Pulmonary rales at auscultation	1.5 (0.7) 2.0	0.5 (1.0) 0.0	< 0.0001
Chest pain while coughing	1.5 (0.6) 1.0	0.7 (0.8) 1.0	< 0.0001
Dyspnoea	0.4 (0.7) 0.0	0.2 (0.6) 0.0	0.2210

Table 29: Change in individual symptoms of the BSS total score (Day 0 – Day 7) (mean (SD), median and two-sided p-value of the t-test; LOCF) (cited from Tribanek and Buschulte, 2008a Study report 70103.01.001)

Study 2:

Patients less than 7 years old FAS (n = 78)			
	EPs® 7630 (n = 39)	Placebo (n = 39)	p-value
Coughing	1.7 (0.9) 2.0	1.2 (0.8) 1.0	0.0038
Pulmonary rales at auscultation	1.9 (0.9) 2.0	1.2 (0.8) 1.0	0.0013
Dyspnoea	1.1 (0.8) 1.0	1.0 (0.7) 1.0	0.5525
Patients between 7 and 12 years old FAS (n = 72)			
	EPs® 7630 (n = 37)	Placebo (n = 35)	p-value
Coughing	1.6 (0.8) 2.0	1.1 (0.9) 1.0	0.0063
Sputum	0.7 (0.8) 1.0	0.0 (0.8) 0.0	0.0006
Pulmonary rales at auscultation	1.9 (0.8) 2.0	1.0 (1.0) 1.0	< 0.0001
Chest pain while coughing	1.1 (1.0) 1.0	1.0 (0.8) 1.0	0.7086
Dyspnoea	0.7 (0.9) 0.0	0.5 (0.6) 0.0	0.2848
Patients above 12 years old FAS (n = 70)			
	EPs® 7630 (n = 35)	Placebo (n = 35)	p-value
Coughing	2.0 (0.8) 2.0	1.4 (0.8) 1.0	0.0019
Sputum	0.7 (0.7) 1.0	0.2 (1.0) 0.0	0.0090
Pulmonary rales at auscultation	1.7 (1.0) 2.0	0.9 (0.8) 1.0	0.0002
Chest pain while coughing	1.2 (1.0) 1.0	0.9 (0.7) 1.0	0.2127
Dyspnoea	0.7 (0.8) 1.0	0.7 (0.8) 0.0	0.8832

Table 30: Change in individual symptoms of BSS total score (Day 0 - Day 7) (mean (SD), median and two-sided p-value of the test; LOCF) (cCited from Tribanek and Buschulte, 2008b Study report 70103.01.004)

The tables above show (table 29, 30) the changes of the individual symptoms of the BSS total score between baseline and the end of the treatment phase. All items in three subgroups showed more pronounced reduction in the treatment group as compared to the placebo group. In study 1 the items "coughing" and "pulmonary rales at auscultation" were significantly more improved in patients treated with EPs® 7630 as compared to the placebo groups in all subgroups. The item "chest pain" while coughing" collected in patients aged 7 years and above showed significant advantages of EPs® 7630 for both subgroups. In Study 2 the items "coughing" and "pulmonary rales at auscultation" were significantly more improved in patients treated with EPs® 7630 as compared to the placebo groups in all subgroups as well the item "sputum" in patients between 7 and 12 and above 12 years.

Assessor's comment:

Although the differences between the treatment groups in more individual items of BSS score were statistically significant, but clinically they were not. At least one point difference between the two treatments can be considered as clinically relevant effect.

Open studies

Haidvogl *et al*. (Haidvogl and Heger, 2007) (Haidvogl *et al*., 1996) 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 13).

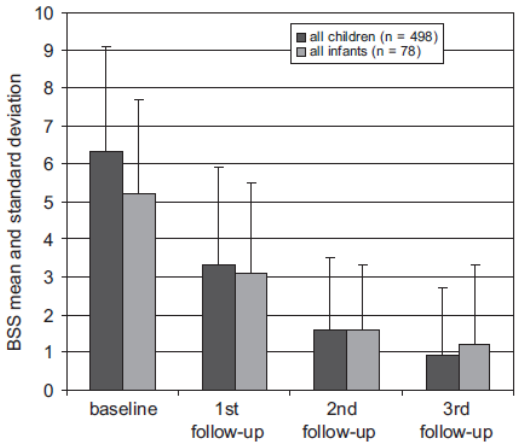


Figure 13: BSS changes during the study period in children and infants. (Matthys *et al*., 2007)

Thirteen out of 420 adverse events occurred in children and 3 out of 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.

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%.

Haidvogl and Heger (2007) referred an uncontrolled observational study carried out by Dome and Schuster. The efficacy of EPs® 7630 treatment (5-20 x 3 drops daily) of acute bronchitis or acute exacerbation of chronic bronchitis in 259 children with the preparation from *Pelargonium* roots was examined in 53 paediatric practices. The BSS decreased from 6.0±2.9 points to 2.3±2.8 points within 2 weeks. Remission or improvement rates of the individual symptoms were more than 80%. In 96.5% of the cases, physicians assessed tolerability of the treatment as very good or good. Only a few mild- and short-termed adverse events were recorded (Dome and Schuster, 1996).

- **Tonsillopharyngitis**

In a multicentre, prospective, randomised, 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, rubor 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® 7630 and placebo were at 60-79% and 47-27%, respectively, followed by sore throat with 32 and 16% and rubor 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%) 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; Neidig, 2002c).

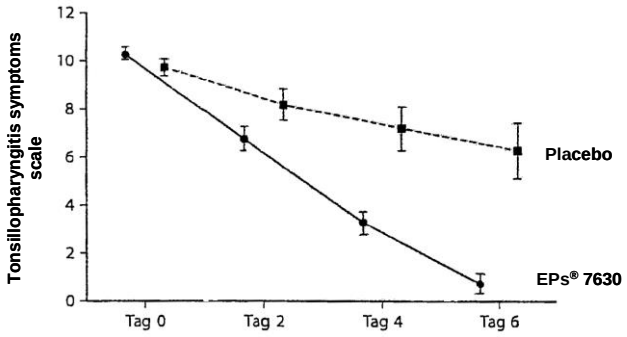


Figure 14. Decrease of the Tonsillopharyngitis Severity Score in the course of a 6-day therapy (Heger and Bereznoy, 2002) (Bereznoy *et al*. 2003)

Acute angina catarrhalis

In a multicentre, prospective, randomised, placebo-controlled study patients aged 6-10 years with acute angina catarrhalis were recruited. 60 patients were treated with EPs® 7630 (3 x 20 drops daily), 64 with placebo. The primary variable for assessing efficacy was the change from baseline of the total score of angina-specific symptoms (five symptoms, including difficulty in swallowing, sore throat, salivation, erythema, fever) on day 4. In the EPs® 7630 group the angina-specific score decreased with 6.7±2.8 compared to the mean decrease of 3.8±4.2 in the placebo group which confirmed the efficacy of the active treatment over placebo. Also, higher efficacy of EPs® 7630 in comparison with placebo was observed taking into account the single angina-specific symptoms. 49 out of 60 patients were

symptom-free or experienced a strong improvement of their symptoms after EPs® 7630 therapy. In contrast, this proportion was only 19 out of 64 in the placebo group (Neidig, 2002b).

Study	Design	Study population	Treatment	Endpoints	Results (*Pelargonium* extract vs. placebo/comparator)
Kamin *et al*. 2010a (Malek et al., 2007b Study report)	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 advers events	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 hour 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
Romberg, 2004b	MC, C, R, DD	**ACUTE BRONCHITIS** present <48 hours BSS ≥5 points n=213 age: 6-12 years	104 patients EPs 7630 20x3 times daily 109 patients acetylcystein 2x200 mg daily duration: 7 days	1st reducion of BSS on day 7 2nd adverse events	6.7±2.1 vs. 6.6±2.3 4.8% vs. 9.2% of the patients
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
Malek 2007a Kamin *et al.*, 2010b, 2012 (Study 1) **Malek 2007d (study 2)**	DB, PC, R	**ACUTE BRONCHITIS** present < 48 hours BSS ≥ 5 points n(1)= 200 n(2)=220 age: 1-18 years mean age: 9	study 1: 103 patients Study 2: 111 patients EPs® 7630 1-6 years: 3x10 drops 6-12 years: 3x20 drops 12-18 years: 3x30 drops Placebo	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%)

Schulz, 2008b (Study 1 and 2)			Study 1 97 patients Study 2:109 patients duration: 7 days		
Heger and Bereznoy, 2002; Bereznoy *et al*. 2003 (also in Neidig, 2002c)	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%
Neidig, 2002b	MC, R, DB, PC	non-Streptococci-induced **ACUTE ANGINA CATARRHALIS** present <48 hours n=124 age: 6-10 years mean age: 7.5 46% male	60 patients EPs® 7630 20 drops, 3 times daily 64 patients placebo duration: 4 days	1st change of total score of angina-specific symptoms on day 4 2nd adverse events	6.7±2.8 vs. 3.8±4.2 6.7% vs. 25.0%

Table 31: clinical studies with *Pelargonium* extract– children

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

4.3. Overall conclusions on clinical pharmacology and efficacy

This assessment report presents seven clinical studies (including two dose-finding trial) Romberg, 2004d – UM037; Malek *et al*., 2007c Study report No: 701003.01.003 pubished by Schulz, 2008a; Matthys, 2010a and b; Neidig *et al*., 2002 clinical report-UM26, published by Glovatiouk and Chuchalin, 2002; Chuchalin *et al*., 2005 and Schulz, 2007; Romberg 2004c clinical report-UM 27 published by Matthys *et al*., 2003; Romberg, 2004a clinical report-UM 28 published by Matthys and Heger, 2007a; Matthys and Funk, 2008 which examined the efficacy and safety of *Pelargonium sidoides* extract in adult patients with acute bronchitis.

Two comperative studies with acetylcisteine and three placebo controlled clinical trials (including one dose-finding study with tablets) performed with *Pelargonium* extract EPs® 7630 in children with acute bronchitis were evaluated (Blochin *et al*., 1999; Romberg, 2004b-UM009 clinical trial report; Malek, 2007a Study No.701003.01.001 published by Kamin *et al*., 2010; Matthys and Kamin, 2011; Schulz, 2008; Malek *et al*., 2007d Study no.701003.01.004; Schulz, 2008; Malek *et al*., 2007b Sudy report 701003.001.002 published by Kamin *et al*., 2010a) in detail as well.

All clinical studies used the same methods to measure the effectivness of EPs® 7630 preparation comparing to placebo or to the comperator. The primary outcome criterion was the change of Bronchitis Severity Score (BSS) from baseline to Day 7 (arithmetic mean, Day 7-minus Day 0). The BSS total score consists of the five symptoms coughing, sputum production, pulmonary rales/rhonchi at auscultation, chest pain while coughing and dyspnoea, which are the most important features associated with acute bronchitis, rated on a scale from 0 (not present, mild, moderate, severe, very severe) to 4 and leading to a maximum total score of 20 points.
When the studies were performed the BSS score was not validated but appeared to be associated with a clinical benefit (Kamin *et al*., 2010a). It should be pointed out, there are validated scores to assess the efficacy in similar conditions (Mwachari *et al.* 2007).

The Cochrane review on *Pelargonium sidoides* also drew attention to the fact that the studies used non-validated symptom scores as a primary endpoint. 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 and 2013), but more well-designed, placebo controlled trials with endpoints such as time to complete recovery, lost days of work, and use of antibiotics were recommended. It would be desirable if the available manufacturer-initiated studies from Eastern Europe could be complemented by more evaluations from independent researchers covering a larger variety of settings and methodological approaches.

After the publishing the first Assessment report on Pelargonii radix the marketing authorisation holder of EPs® 7630 submitted to the Committee a document consisting in a retrospective validation of Bronchitis Severity Score (BSS) (Lehrl 2012).
Following the assessment of newly submitted data on the validity of the Bronchitis Severity Scale (BSS) in clinical evaluation of medicines used in patients in the therapeutic area 'cough and cold', the HMPC considered the BSS to be an acceptable, valid measurement instrument (7 June 2013, EMA/HMPC/301544/2013).
Since the acceptance of BSS validity could not be translated automatically into acceptance of acute bronchitis as indication or acceptance of well-established use it was agreed that starting from July 2013, the HMPC would check consequences for existing monographs in this therapeutic area, according to each respective data situation, in line with the 'Reflection paper on the reasons and timelines for revision of final European Union herbal monographs and European Union list entries.

Although all placebo controlled clinical studies performed in acute brochitis in adults concluded that the differences between the decrease of the BSS score comparing the EPs® 7630 with placebo (7.2-4.9 = 2.3, 5.9-3.2 = 2.7, 7.6-5.3 = 2.3) were statistically significant ($p<0.0001$, each) these differences can not be considered as clinically relevant. Since acute bronchitis is a self-limited condition with great placebo effect at least difference of 4 points (20% of the total symptoms score) between the effect of EPs® 7630 and of placebo is desirable.
The result of UM 37 dose-finding clinical study (Romberg, 2004d) for the 3 x 30 drops treatment group where the difference was greater, 6.3, cannot be considered because the a great number of withdrawals (see Table 10).

The same opinion was drawn from the studies conducted in children.

The two comparative studies with acetylcysteine have methodical failures. In the first study with patients 7-14 years of age the authors did not give information about withdrawals. The two treatment groups were not homogenous in gender distribution and seriousness of cough and sputum. The posology was not in line with the product information. 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.

The second study could have been a three-arm study with a placebo arm besides the EPs® 7630 and acetylcysteine group, since the study was double dummy and placebos were available for EPs® 7630 and for acetylcysteine as well. Patients in the EPs® 7630 group took acetylcysteine placebo as well and in acetylcysteine group received EPs® 7630 placebo as well. The two treatment groups were not homogenous in the aspect of previous ear, nose and throat (ENT) infection. At baseline the patients in EPs® 7630 group had less frequently reported previous ENT infections, prevoius treatment of ENT infections, if necessary, and concomitant diseases including respiratory disorders. Previous medication had to stop less frequently before start of the trial in the EPs® 7630 group. On average the social level was higher in the EPs® 7630 group than in the acetylcysteine group.

Concerning the placebo controlled study they were not planned dealing with the age groups separately (patiens between 1-6, 7-11 and 12-18 years of age). Although post-analysis were performed and the results showed statistically hihgh difference between the EPs® 7630 and placebo group, but not clinically relevant since the difference between the two treatment groups did not reach the 20% of the total score.
In the case of total 12 points of BSS 2.4 points of difference can be considered clinically relevant. The difference between the two treatment groups was only 3.1–0.9 = 2.2 in study 1; 4.6-3.3 = 1.3 in study 2 for the age group below 7 years of age.
In the case of total 20 points of BSS 4.0 points of difference can be considered clinically relevant. The difference between the two treatment groups is only 5.6-2.3 = 3.3 in study 1; 6.0-3.5 = 2.5 in study 2 for the age group between 7-12 years of age. For the age group above 12 years of age the difference is 4.9-1.8 = 3.1 in study 1; 6.3-4.0 = 2.3 in study 2.

Furthermore some of the clinical studies showed methodical deficiencies. For example the treatment groups were not homogenious from all aspects which could have impact on the results (see the detailed evaluation at each study.)

Although, according to the authors, the clinical relevance of difference in favour of EPs® 7630 is underlined by the results for all evaluable secondary efficacy parameters showing the same tendency, but clinicaly relevant difference between EPs® 7630 and placebo should be presented for the primary outcome criterion.
Although the results of open studies are also promising, the lack of true control group, blinding and randomisation limits the usefulness of these trials.

The evaluation of the effects of the drug in adult patients with acute sinusitis was based on three trials (Schapowal and Heger, 2007; Bachert *et al*. 2009; Romberg, 2004e). 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, more trials using validated instruments are needed 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 the preparation from *Pelargonium* 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).

One clinical trial was conducted to assess the safety and tolerability of long-term administration of EPs® 7630 in 2 different dosages over 6 weeks compared to placebo in healthy volunteers (18-55 years). The study was performed as a prospective, randomised, double-blind, placebo-controlled, monocenter clinical trial in a parallel group design with 24 subjects per treatment group. The trial

consisted of a screening with pre-trial examinations prior to enrolment followed by a 6 weeks double-blind treatment period. The subjects were randomly assigned to one of three treatment groups. Group I (24 subjects) received EPs® 7630, 3 x 30 drops, group II (24 subjects) EPs® 7630, 3 x 60 drops, Group IIIa (12 subjects) placebo, 3 x 30 drops, group IIIb (12 subjects) placebo, 3 x 60 drops. The mean duration of treatment was 41.5±2.8 days.

The number of advers events in the EPs® 7630 high dose group (33 advers events in 18 out of 24 subjects (75%)) was slightly higher than in the EPs® 7630 low dose group (31 advers events in 15 out of 24 subjects (62.5%)) and the placebo group (28 advers events in 13 out of 24 subjects (54.2%)). Most of the advers events [29 out of 33 (87.9%) in the EPs® 7630 high dose group, 30 out of 31 (96.8%) in the EPs® 7630 low dose group and 24 out of 28 (85.7%) in the placebo group] were assessed as "not related" to the trial medication. For 9 out of 92 (9.8%) advers events [4 out of 33 (12.3%) in the EPs® 7630 high dose group, 1 out of 31 (3.2%) in the EPs® 7630 low dose group and 4 out of 28 (14.3%) in the placebo group] a causal relationship with the investigational medication could not be excluded. Most of the advers events were of mild or moderate intensity. One patient in the EPs® 7630 high dose group and three subjects in the EPs® 7630 low dose group experienced advers events of severe intensity; all of them were considered as "not related" to the investigational medication. There were no serious adverse events during the course of the study. Mean values of laboratory parameters (haematology, chemistry and coagulation parameters), urinanalyis, vital signs and ECG did not show any relevant change throughout the trial (Zind *et al*. 2011).

5.2. Patient exposure

The clinical trials referred in assessment report were conducted on over 3500 adult patients and approximately 3,000 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) summarised 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 corresponding 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. EPs® 7630 is marketed as medicinal product in the European Union and therefore it is bound to a pharmacovigilance system.

The safety profile of EPs® 7630 has been systematically reviewed based upon 25 clinical trials and post-marketing surveillance studies with 9,218 patients suffering from acute or chronic respiratory tract infections such as bronchitis, tonsillopharyngitis, broncitis or sinusitis and from 31 healthy

subjects. EPs® 7630 was well tolerated and no serious adverse drug reactions were reported. Comparing EPs® 7630 and placebo, adverse events were similar with regard to quality and quantity throughout almost all organ systems and symptoms, the only difference being a slightly higher incidence of gastrointestinal disorders (epigastric pain, nausea, diarrhoea) and of hypersensitivity reactions (mostly skin reactions), as well as gingival bleeding and epistaxis associated with EPs® 7630 compared to placebo (Matthys and Köhler, 2010).

The Uppsala Monitoring Centre, in conjunction with the international pharmacovigilance program of the World Health Organisation, 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, diarrhoea, 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 an 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 dyspnoea 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. None of the coumarin compounds so far identified in the preparation from *Pelargonium* roots used in this *in vivo* experiment meets the criteria of minimal structural requirements for anticoagulant characteristics in coumarins, which would correspond to a hydroxy group in position 4 and a non-polar rest in position 3. Indeed, no anticoagulant effects were observed in this study. In addition, it could be demonstrated that comedication has no effect on the pharmacokinetics of warfarin (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 dechallenge, 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.

A case of primarily assumed liver injury in connection with the use of *Pelargonium* has been reported by the Drug Commission of the German Medical Association (DCGMA) and it was assumed that other cases of liver disease might be attributable to the treatment. Therefore, reports of spontaneous cases of purported *Pelargonium* hepatotoxicity were reviewed to assess data quality and causality as originally presented since 2004. The study group consisted finally of 15 patients originating from Germany and included cases of spontaneous reports with liver disease in primarily assumed temporal and causal association with the treatment by *P. sidoides*. *Teschke et al* re-evaluated the data of these patiens to assess the causality. The data of all 15 cases were submitted to a causality algorithm that consisted of four steps: assessment of key items related to a temporal association (step 1), criteria of *Pelargonium* hepatotoxicity and definition of the pattern of liver injury (step 2), application of a liver specific, quantitative, and structured causality assessment method (step 3), and exclusion of alternative diagnoses (step 4). Evaluations considered not only *Pelargonium* but also synthetic drugs, herbal drugs, and dietary supplements, summarised as comedicated drug(s). The analysis revealed confounding factors such as numerous final diagnoses unrelated to *Pelargonium* and poor data quality in several cases. In only a minority of the cases were data provided to consider even common other diseases of the liver. For instance, biliary tract imaging data were available in only 3 patients; data to exclude virus infections by hepatitis A-C were provided in 4 cases and by CMV and EBV in 1 case, whereas HSV and VZV virus infections remained unconsidered. The assessment showed lack of convincing evidence for a hepatotoxic risk associated with the treatment of *Pelargonium* when the present spontaneous reports were analysed and *Pelargonium* use was as recommended. In none of the 15 analysed cases could *Pelargonium* hepatotoxicity be confirmed as the final diagnosis (Teschke *et al.* 2012a).

In a subsequent publication (Teschke *et al*. 2012b), it was examined whether and to what extent treatment by *Pelargonium* was associated with the risk of liver injury in further 13 spontaneously reported hepatotoxicity cases. The patients originated from Germany (9), Switzerland (2), Italy (1) and Singapore. Their data were submitted to a thorough clinical evaluation that included the use of the original and updated scale of CIOMS (Council for International Organisations of Medical Sciences) to assess causality levels. These scales are liver specific, validated for liver toxicity, structured and quantitative. According to the analysis, none of the 13 spontaneous cases of liver disease generated a positive signal of safety concern, since causality for Pelargonium could not be established on the basis of the applied CIOMS scales in any of the assessed patients. Confounding variables included comedication with synthetic drugs, major comorbidities, low data quality, lack of appropriate consideration of differential diagnoses, and multiple alternative diagnoses. Among these were liver injury due to comedication, acute pancreatitis and cholangitis, acute cholecystitis, hepatic involvement following lung contusion, hepatitis in the course of virus and bacterial infections, ANA positive autoimmune hepatitis, and other preexisting liver diseases. In the course of the case assessments and under pharmacovigilance aspects, data and interpretation deficits seemed to be evident for the authors. Consequently, the authors ascertained lack of hepatotoxicity by *Pelargonium* in all 13 analysed spontaneous cases (Teschke *et al*. 2012b).

Until June 2012, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM, Germany) received 30 spontaneous reports (26 from Germany, 2 from Switzerland, 1 from Italy and 1 from Singapore) on the hepatic adverse effects (11 hepatitis, 8 icterus, 3 hepatic injury) associated with *Pelargonium* product application. One patient suffering from hepatitis has had liver transplantation. In 7 hepatitis cases, the association of hepatitis and *Pelargonium* consumption was evaluated to be possible, in 1 case possible-probable, in 1 case probable. In case of icterus, the association was evaluated to be possible in 6 cases and probable in 2 cases. From the 3 hepatic injury cases 2 were evaluated to be possibly associated with *Pelargonium* application. In 19/30 cases there was reported co-medication.

BfArM concluded that there is at least a possible association between *Pelargonium* application and hepatotoxicity and therefore a Graduated Plan came into force to minimise risks and a post authorisation safety study was requested for the further assessment of the hepatotoxic risk.

The Summary of Product Characteristics of the products marketed in Germany has to be supplemented with the following (BfArM, 2012):

> Special warnings and precautions for use: "Hepatotoxicity and hepatitis cases were reported in association with the application of <product name>. In case of signs of hepatotoxicity occur, the application of <product name> should be stopped immediately and a medical doctor should be consulted."
>
> Undesirable effects: "Hepatotoxicity and hepatitis cases were reported in association with the application of <product name>. Since these cases were reported spontaneously, the frequency is not known."

Taking into account the possible association between the use of *Pelargonium* and hepatotoxicity *'Pelargonium sidoides dc and / or Pelargonium reniforme curt., radix* was put on the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs). The PSUR cycle is 5 yearly the next data lock point is 01.06.2018. PSURs are required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended except for products referred in Article Article 14 of Directive 2001/83/EC as amended.

Assessor's comment:

A full set of information will be collected for this PSUR evaluation procedure so the revision of this part of the Assessment report will be performed after the end of this procedure.

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.

In a review os clinical trials and post-marketing studies involving 9,218 patients, data on treatment-emergent changes in liver enzymes from placebo-controlled trials gave no indication of an unfavourable influence of EPs® 7630 (Matthys and Köhler, 2010).

In spontaneous hepatotoxicity reports, liver enzyme deviations were documented in some cases. Among the 13 cases assessed in the paper of Teschke *et al.* 2012b, values of ALT, AST and ALP were available in 8, 6 and 5 cases, respectively. ALT was on average 1041 U/L (101-2500), with AST, the average was 1288 U/L (49-4000) and ALP showed an average value of 140 U/L (63-178). ALT values following *Pelargonium* cessation were restorted in 6 cases and found decreased, but in none of the overall 13 patients ALT normalisation has been reported (Teschke *et al*. 2002b).

Among the 15 study patients analysed by Teschke et al. (Teschke *et al.* 2012a), values of ALT, AST, and ALP were available in 12, 11, and 6 cases, respectively. ALT was on average 1124 U/L with a range of 68 to >3000 U/L; with AST, the average was 827 U/L and the range from 70 to >3000 U/L; and ALP showed an average value of 215 U/L with a range of 144 to 319 U/L. In only 4 patients ALT normalisation was reported. In none of the 15 cases were the liver values presented for the time before *Pelargonium* use to verify lack of preexisting hepatobiliary diseases. In a single patient, however, increased aminotransferases of ALT 196 U/L and of AST 54 U/L were still observed 6 months following cessation of PS.

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 (C_{max}) 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) (Arold and Wollny, 2003; Roots *et al*. 2004).

On the basis of available non-clinical and limited clinical data, it can be ssumed that *Pelargonium* preparations do 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 been performed.

No information is available on overdose, drug abuse and withdrawal. The ethanol content of preparations from *Pelargonium* roots 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 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 liquid 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. The dry extract equivalent to the above mentioned liquid extract (dry extract, (DER 4-25:1), extraction solvent ethanol 11% (m/m)) is also included in the traditional use monograph.

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

Due to insufficient published data on toxicity the inclusion of Pelargonii radix in the European Union list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

Annex

List of references