29 May 2024
EMA/HMPC/765656/2022
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix

Final - Revision 2

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)		*Pelargonium sidoides* DC; *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) Dry extract (DER 4-7:1), extraction solvent ethanol 14% (V/V)
Pharmaceutical form(s)		Herbal preparations in liquid or solid dosage forms for oral use.
First assessment	Rapporteur	Z. Biró-Sándor
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1. Introduction

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

- Herbal substance(s)

According to the European Pharmacopoeia (01/2024:2264), *Pelargonium* root (Pelargonii radix) is defined as the dried, usually fragmented underground organs of *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix.
Content: minimum 2.0 per cent of tannins, expressed as pyrogallol ($C_6H_6O_3$; Mr 126.1) (dried drug).

The characteristic constituents of *Pelargonium* species include a series of simple coumarins (Kayser and Kolodziej, 1995) and combined oxygenation typical for the genus *Pelargonium* (Kolodziej, 2000).

Structural examination of root metabolites of *Pelargonium* species led to the characterisation of other 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).

- Herbal preparation(s)

No pharmacopoeia monographs are available for preparations from Pelargonium roots.

Schnitzler *et al.* (2008) analysed the compounds of aqueous root extract of *P. sidoides* by LC-MS spectroscopy; the major constituents in *Pelargonium* extract were glucogallin, fraxetin-7-O-glucoside, catechin, dihydroxy-coumarin-sulfate, fraxetinsulfate, monohydroxy-dimethoxycoumarin, dihydroxy-dimethoxycoumarin, dihydrokaemferol, umckalin.

- 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.

1.2. Search and assessment methodology

This Assessment Report resulted from the systematic review of that previously issued (EMA/HMPC/444251/2015) considering the new information from data published in the literature between 2018 and 2022.

The First revision of the original Assessment report followed the acceptance of the Bronchitis Severity Score (BSS) by the HMPC as a validated tool based on newly submitted data in 2013 and was solely focused on the reconsideration of available clinical data.

Search engines used: Google, Google Scholar

Scientific databases: Web of Science; PubMed; Science Direct; Clinical Key; Cochrane Database of Systematic Reviews

Medical or Toxicological databases: Toxline

Search terms: Pelargonium sidoides, Pelargonium reniforme, Umckaloabo (2018-2022).

Pharmacovigilance resources: Data from EU and non-EU regulatory authorities, European database for suspected adverse drug reaction reports. Search terms: Pelargonium sidoides, "Pelargonium reniforme, Umckaloabo. This assessment report covers the PSURs submitted for the active substance for a reporting period of 10 years, spanning from 2 June 2013 to 1 June 2018 and 2 June 2018 to 1 June 2023.

Data from EU and non-EU regulatory authorities: Assessment report on *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix - (EMA/HMPC/444251/2015)

Other resources: No data was provided by the interested parties.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
Liquid extract (1:8-10); extraction solvent: ethanol 11% (m/m)	Common cold	*Oral liquid* (1 ml=21 drops. 10 g (=9.75 ml) liquid contain 8 g extract) Children 1-5 years: 3 times daily 10 drops Children 6-12 years: 3 times daily 20 drops Adults and adolescents over 12 years: 3 times daily 30 drops	TU (2007, Austria) TU (2009, Belgium) TU (2013, Croatia) TU (2007, 2013, The Netherlands) TU (2009, Spain)[a] TU (2009, Sweden)[a]
	Symptomatic treatment of acute bronchitis, expectoration relief		MA (1997, Lithuania)
	Symptomatic treatment of acute bronchitis not requiring antibiotic therapy	*Oral liquid* (1 ml=21 drops. 10 g (=9.75 ml) liquid contain 8 g extract) Children 1-5 years: 3 times daily 10 drops Children 6-12 years: 3 times daily 20 drops Adults and adolescents over 12 years: 3 times daily 30 drops Duration of use: 7–10 days	MA (2008, Czech Republic)

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
	Acute bronchitis	*Oral liquid* (1 ml=21 drops. 10 g (=9.75 ml) liquid contain 8 g extract) Children 1-5 years: 3 times daily 10 drops Children 6-12 years: 3 times daily 20 drops Adults and adolescents over 12 years: 3 times daily 30 drops No longer than 3 weeks.	MA (1976, 2006, Germany)
Dry extract from *Pelargonium sidoides* DC, *radix* (DER 1:8–10); extraction solvent: ethanol 11% (m/m)	Common cold	*Film-coated tablets* (20 mg extract per tablet) Adults and adolescents over 12 years: 3 times daily 1 tablet	TU (2009, Austria) TU (2010, Italy) TU (2009, Spain)
		Film-coated tablets Children 6-12 years: 1 tablet 2 times daily Adults and adolescents over 12 years: 1 tablet 3 times daily	TU (2013, Croatia) TU (2009, The Netherlands)
		Tablets (20 mg extract per tablet) Children 6-12 years: 1 tablet, 2 times daily (morning, evening) Adults and adolescents over 12 years: 1 tablet 3 times daily (morning, noon, evening) Tablets to be taken with some liquid; do not chew. *Syrup* (0.25 g extract per 100 g syrup) Children 1-5 years: 2.5 ml, 3 times daily Children 6-12 years: 5 ml, 3 times daily Adults and adolescents over 12 years: 7.5 ml, 3 times daily Average duration of administration is 7 days. Continue the	TU (2009, 2013, Belgium)

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
		treatment for some days when symptoms are decreasing. Maximal duration: 3 weeks.	
	Symptomatic treatment of acute bronchitis	*Film-coated tablets* Adults and adolescents over 12 years: 3 times daily 1 containing 20 mg extract	MA (2009, Germany) MA (2012, Lithuania)
Dry extract of Pelargonii radix (4-25:1); extraction solvent: ethanol 11% (m/m)	Symptomatic treatment of acute bronchitis	*Syrup* (0.2506 g/100 g - 93.985 ml) Children 1-6 years: 2.5 ml 3 times daily Children 7-12 years: 5 ml 3 times daily Adults and adolescents over 12 years: 7.5 ml 3 times daily No longer than 3 weeks.	MA (2010, Germany)
Dry extract of Pelargonii radix (4-7:1); extraction solvent: ethanol 14% (V/V)	Common cold	*Film-coated tablets* (20 mg) Children 6-12 years: 1 tablet, 2 times daily Adults and adolescents over 12 years: 1 tablet, 3 times daily No longer than 3 weeks.	TU (2013, Germany)
Dry liquid extract of root; 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	Common cold	*Film-coated tablets* Children 6-12 years: 1 tablet 2 times daily Adults and adolescents over 12 years: 1 tablet 3 times daily	TU (2009, Sweden)
	Symptomatic treatment of acute bronchitis	*Syrup* (0.2506 g/100 g = 93.985 ml) Children 1-6 years: 2.5 ml 3 times daily Children 7-12 years: 5 ml 3 times daily Adults and adolescents over 12 years: 7.5 ml 3 times daily No longer than 3 weeks.	MA (2010, Germany)

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
liquid extract from *Pelargonium sidoides, radix* (1:8–10); extraction solvent: ethanol 15% (V/V)	Common cold	*Syrup* (100 g syrup containing 0.25 g dried extract) Children 6-12 years: 5 ml syrup, 3 times daily	TU (2013, The Netherlands)
		Oral drops Children 6-12: years: 793 mg (= 0.78 ml) liquid extract 3 times daily Elderly, adults and adolescents above 12 years: 1186 mg (= 1.15 ml) liquid extract 3 times daily	TU (2011, Sweden)
Liquid extract from *Pelargonium sidoides* DC, radix (1:8-10); extraction solvent: ethanol 11% (m/m) (EPs 7630)	Acute infections of the respiratory tract and the ear-nose-throat region such as bronchitis and sinusitis. Acute infections of upper airways, such as symptomatic treatment of common cold. Use in case of acute and chronical infections, especially infections of respiratory tract and ear, throat and nose (bronchitis, sinusitis, tonsilitis, rhinopharingitis).	*Oral drops*, solution Children 1-5 years: 10 drops three times per day Children 6-12 years: 20 drops three times per day Adults and adolescents above 12 years: 30 drops 3 times daily. Treatment duration should not exceed 3 weeks	MA (2007, Bulgaria) MA (2000, Latvia) MA (2008, Romania)[a]
	Common cold	*Oral drops*, solution Children 6-12 years: 20 drops three times per day Adults and adolescents above 12 years: 30 drops 3 times daily	TU (2009, Hungary) TU (2010, Italy)
Fluid extract from *Pelargonii sidoides* (1:8–10); extraction solvent: ethanol 11% (m/m) (EPs 7630)	Symptomatic treatment of acute bronchitis not requiring antibiotic therapy	*Film-coated tablets* (20 mg in 1 tablet) Children 6-12 years: 1 tablet twice daily Adults and adolescents over 12 years: 1 tablet 3 times daily Duration of use: 7–10 days	MA (2015, Czech Republic)

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
		Syrup (0.2506 g of dry extract in 100 g of the product) Children 1–5 years: 2.5 ml corresponding to 6.67 mg of dried liquid extract 3 times daily Children 6–12 years: 5 ml corresponding to 13.33 mg of dried liquid extract 3 times daily Adults and adolescents over 12 years: 7.5 ml corresponding to 20 mg of dried liquid extract 3 times daily Duration of use: 7–10 days	
Fluid extract from *Pelargonii sidoides* (1:8–10); extraction solovent: ethanol 11% (m/m) (EPs 7630), dried	Symptomatic treatment of acute bronchitis not requiring antibiotic therapy	*Film-coated tablets* (20 mg in 1 tablet) Children 6–12 years: 1 tablet twice daily Adults and adolescents over 12 years: 1 tablet 3 times daily; Duration of use: 7–10 days	MA (2015, Czech Republic)
	Common cold		TU (2010, Italy)
Fluid extract from *Pelargonii sidoides* (1:8–10); extraction solovent: ethanol 11% (m/m) (EPs 7630), dried	Symptomatic treatment of acute bronchitis not requiring antibiotic therapy	*Syrup* (0.2506 g in 100 g of the product) Children 1–5 years: 2.5 ml corresponding to 6.67 mg of dried liquid extract 3 times daily Children 6–12 years: 5 ml corresponding to 13.33 mg of dried liquid extract 3 times daily Adults and adolescents over 12 years: 7.5 ml corresponding to 20 mg of dried liquid extract 3 times daily Duration of use: 7–10 days	MA (2015, Czech Republic)
Tincture of *Pelargonium sidoides* DC (drug to extraction solvent ratio 1:10); extraction solvent: ethanol 15% (V/V)	Symptomatic treatment of acute bronchitis not requiring antibiotic therapy	*Oral drops* (80 g in 100 ml =100 g) Children 1–5 years: 10 drops corresponding to 0.381 g of the tincture 3 times daily Children 6–12 years:	MA (2013-2016, Czech Republic)

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
		20 drops corresponding to 0.762 g of the tincture 3 times daily Adults and adolescents over 12 years: 30 drops corresponding to 1.143 g of the tincture 3 times daily Duration of use: 7–10 days	
	Common cold	*Oral liquid* (16.48 g/20 ml =20.6 g) 6-12 years: 20 drops 3 times daily Adults and adolescents over 12 years: 30 drops 3 times daily No longer than 3 weeks.	TU (2013, Germany)
Tincture of Pelargonii radix (1:8-9); extraction solvent: ethanol 15% (m/m)	Common cold	*Oral liquid* (16.48 g/20 ml =20.6 g) 6-12 years: 20 drops 3 times daily Adults and adolescents over 12 years: 30 drops 3 times daily No longer than 3 weeks.	TU (2013, Germany)

[a] children from 6 years of age

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Not applicable.

Information on other products marketed in the EU/EEA (where relevant)

Not applicable.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

Pelargonium species (Geraniaceae) indigenous to areas of southern Africa are highly valued by traditional healers for their curative properties since ancient times. Whereas *Pelargonium* species

represent very popular ornamental plants in Europe, infusion of the roots of *P. sidoides* DC and *P. reniforme* Curt. have been used to treat coughs, chest problems including tuberculosis and gastrointestinal (GI) disorders such as diarrhoea and dysentery in Southern Africa. 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 in 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). *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".

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. For nine 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 and Wagner, 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 (EPs 7630). 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). Moreover, the literature search shows that EPs 7630 is largely used for acute bronchitis in both adults and pediatric population (Wopker *et al.,* 2020).

The monograph of Pelargonium root (Pelargonii radix) was introduced into the European Pharmacopoeia in 2008 (last version European Pharmacopoeia 11th ed. 2024).

Outside Europe, various liquid and solid preparations are available as herbal supplements especially in North America and Mexico. *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix

Table 2: Overview of historical data

Herbal preparation	Documented Use/ Traditional Use	Pharmaceutical form Strength Posology Duration of use	Reference
Powdered root	Tuberculosis treatment	Boiled root preparation to drink twice daily	Bladt and Wagner, 2007 (citing BMA, 1909)
Powdered root, Ethanolic liquid extract (with glycerine), Fluid extract, Tincture	Cough remedy	Tincture to be added to a cup of hot water and taken half an hour before a meal twice daily	Helmstädter, 1996

2.3. Overall conclusions on medicinal use

The information about therapeutic indications of preparations from Pelargonium radix is available from literature and from the market overview, which shows the internal use of Pelargonium preparations for acute infection of upper airways common cold and symptomatic treatment of acute bronchitis.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Liquid extract (1:8-10), extraction solvent: ethanol 11% (m/m)	Acute bronchitis	*Oral liquid* (1 ml=21 drops; 10 g (=9.75 ml) liquid contain 8 g extract) Children 1-5 years: 3 times daily 0.4 ml Children 6-12 years: 3 times daily 0.9 ml Adults and adolescents over 12 years: 3 times daily 1.4 ml	MA 1976
Dry extract of Pelargonii radix (4-25:1), extraction solvent: ethanol 11% (m/m) Dry extract of Pelargonii radix (4-7:1), extraction solvent: ethanol 14% (V/V)	Common cold	*Film-coated tablets* (20 mg extract/tablet) Children 6-12 years: 1 tablet 2 times daily Adults and adolescents older than 12 years: 1 tablet 3 times daily *Syrup* (0.25 g extract per 100 g syrup) Children 1-5 years: 6.7mg, 3 times daily Children 6-12 years: 13.3mg, 3 times daily Adults and adolescents over 12 years: 20mg, 3 times daily	TU 2009

After the acceptance of the Bronchitis Severity Score (BSS) as valid score, the HMPC assessed the

published clinical studies (Rev.1) and decided that the requirements of well-established medicinal use laid down in Article 10a of Directive 2001/83/EC were not met (see details in section 4.2). Therefore, after the unscheduled Revision 1, the monograph remained unchanged compared with the previous version published on 20.11.2012.

According to the market overview, the Liquid extract (1:8-10), extraction solvent: ethanol 11% (m/m) from Pelargonium radix received a Marketing authorisation (MA) in some member states of the EU, for more than 10 years, with different therapeutic indications (see Table 1). One of the preparations has been on the market for more than 30 years with the indication acute bronchitis (Germany, 1976). However, this indication needs medical diagnosis and supervision, and so, based on other traditional herbal medicinal products with the same composition in other Member States; the following indication can be accepted: *Traditional herbal medicinal product for the symptomatic treatment of common cold*.

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=1.5 ml=1.542 g=1.2336 g native extract=1.1897-1.2492 ml≈1.2 ml native extract.
- 20 drops finished product=1 ml=1.028 g=0.8224 g native extract=0.7932-0.8328 ml≈0.8 ml native extract.
- 10 drops finished product= 0.5 ml=0.514 g=0.411 g native extract≈0.40 ml native extract.

From the aspect of traditional use-in accordance with definition of corresponding product in the Directive 2004/24/EC (Article 16c(2))-the native dry extract can be considered to be equivalent to the above mentioned liquid extract (dry extract, DER 4-25:1, extraction solvent ethanol 11% (m/m) and so it can be included in the traditional use monograph as well. Also, the dry extract (4-7:1), extraction solvent ethanol 14% (V/V) corresponds to the above described preparation and so, it can be included in the MO.

Thus, historical data and documented period of use in the EU support the evidences of traditional use of pelargonium root for:
Symptomatic treatment of common cold:
a) Liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m);
b) Dry extract (DER 4-25:1), extraction solvent ethanol 11% (m/m);
c) Dry extract (DER 4-7:1), extraction solvent ethanol 14% (V/V).

3. Non-Clinical Data

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

The first reports about the mechanism of action of Pelargonium radix in the treatment of tuberculosis (TB) and other respiratory tract infections considered that the activity was more a ‘‘neutralisation or destruction of the tuberculosis toxins’’ rather than a direct bactericidal effect (Bladt and Wagner, 2007). Some recent studies on the antibacterial activity could be taken in account, although no studies related to the primary pharmacodynamics are available.

3.1.1. Primary pharmacodynamics

None reported.

3.1.2. Secondary pharmacodynamics

Immunomodulatory properties

The study by Nöldner and Schötz (2007) aimed to assess the effect of a dry extract from the roots of *Pelargonium sidoides* on the sickness behaviour induced in mice. Sickness behaviour refers t a set of subjective, behavioural and physiological changes that develop in sick individuals during the course of an infection. This behaviour is mediated by pro-inflammatory cytokines and can be induced in experimental animals by the administration of a cytokine inducer such as lipopolysaccharide (LPS).

Male mice were treated with different dosages of LPS before receiving the treatment which corresponded to a dry aqueous-ethanolic extract from the marketed product EPs (animals received by oral route the extract or different subfractions obtained by ultrafiltration, suspended in agarose gel). Statistical analysis of data was performed with the student's t-test.

Results showed that pretreatment of animals with the Pelargonium extract completely counteracted the LPS-induced sickness behaviour signs such as anorexia, depressed activity, listlessness and malaise. Mainly the high molecular weight fraction (> 30kDa) was responsible for this effect. Nonetheless, the molecular basis of this effect was not known.

Although other studies have been performed to evaluate the claimed immunostimulating activity of Pelargonium preparations, all of them were designed as *in vitro* studies, which may be useful but must be interpreted cautiously.

As reported by Willson and Grundmann (2017), the *in vitro* data are of limited relevance when comparing the concentrations necessary to exert meaningful activity in humans after oral administration. Thus, the studies by Kayser *et al.* (2001), Thäle *et al.* (2008), Kolodziej *et al.* (2003), Koch *et al.* (2002), Kolodziej *et al*. (2005), Trun *et al*. (2006), Kolodziej and Kiderlen, 2007), Koch and Wohn (2007), can not support an immunostimulating activity for Pelargonium root. Furthermore, the endotroxin content of the extracts were not investigated/reported, therefore it is not clear, if possible content of high molecular pyrogens influenced immunomodulating properties *in vitro* as investigated by Kruk *et al*. (2021).

Antibacterial and Antimycobacterial 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. Interestingly, at 5-7 mg/ml (MIC), the crude Pelargonium root extracts were found to be moderately active against the tested bacteria, the aqueous extract being the most active. 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.

Acetone and methanol extracts of *P. sidoides* were investigated for antimicrobial activity against 10 bacterial and 5 fungal species by Lewu *et al*. (2006a). The agar medium contained the extracts at final concentrations of 1.0, 2.5, 5.0, 7.5, and 10.0 mg/ml. 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.. 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) at final concentrations of 1.0, 2.5, 5.0, 7.5 and 10.0 mg/ml. 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 efficacy on 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).

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 radio-respiromertric 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*. Activity was much lower than the standard isoniazid, with a MIC value 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. Very low 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.

Assesor's comment:
Some studies have been conducted to test the antibacterial activity of Pelargonium radix preparations and isolated compounds. Nonetheless, the antibacterial activity of pelargonium root is significantly inferior to commercial antibiotics and cannot support an antibiotic effect in the claimed conditions. In any case, as a general guideline for in vitro testing of antibacterial, antifungal and antiparasitic activity,

a stringent endpoint criteria with IC_{50} values below 100 µg/ml for extracts (and below 25 µM for pure compounds) should be used (Butterweck and Nahrstedt, 2012). Results obtained with Pelargonium preparations are far above these levels and thus, their antibacterial activity is much lower.

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

Some studies have been conducted to investigate further activities of Pelargonium radix preparations, such as the ones by Wittschier *et al.* (2007), Brendler and van Wyk (2008), Conrad *et al*. (2007a, b), Conrad and Frank, (2008), Dorfmüller *et al*. (2005), Schnitzler *et al.* (2008) and Neugebauer *et al.* (2005), regarding the effect on bacterial adhesion or antiviral effects, among others.

Nonetheless, no conclusions can be drawn from those *in vitro* studies.

Cytotoxicity

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).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Non-clinical data are mainly coming from *in vitro* studies. Nevertheless, these *in vitro* studies and the published results in animal models are not able to explain the mechanism of action of pelargonium root in the claimed indication. Although several pharmacologically active constituents have been identified (for example gallic acid and its methyl ester), most of the published studies are not well designed, with a lack of positive and negative controls, and moreover, do not support the therapeutic use of the root.

Data on safety pharmacology and pharmacodynamic interactions are not available.

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 isolated 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-

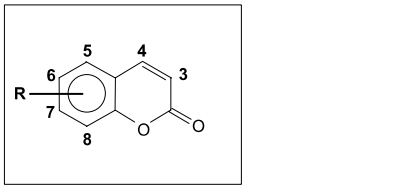
hydroxycoumarin by hepatic CYP2A6. After administration of coumarin, 68-92% of the dose was 7-hydroxycoumarin in urine as glucuronide and sulfate conjugates. While 7-hydroxylation is the main way of coumarin metabolism in humans, the major pathway in most rodents is by 3,4-epoxidation resulting in the formation of ring opened metabolites including o-HPA, o-HPPA. 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).

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).

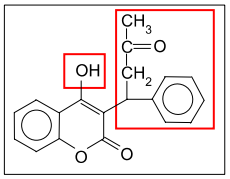
Pharmacokinetic interactions

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 pre-treatment with EPs 7630 for 2 weeks.

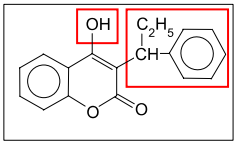
Moreover, the coumarins so far identified in EPs 7630 do not possess the structural characteristics needed for anticoagulant activity. The minimal structural requirements for anticoagulant activity in coumarins are a hydroxyl group in position 4 and a non-polar rest in position 3 (Figure 2).



7-Hydroxy-6-methoxy-
5,6,7-Trimethoxy-
7-Hydroxy-5,6-dimethoxy-
7-Acetoxy-5,6-dimethoxy-
6,8-Dihydroxy-7-methoxy-
6,7,8-Trimethoxy-
5,6,7,8-Tetramethoxy-
6,8-Dihydroxy-5,7-dimethoxy-
5,7-Dimethoxy-7-sulfat-
8-Hydroxy-5-7-dimethoxy-6-sulfat-
6-Hydroxy-5,7-dimethoxy-8-sulfat-



Warfarin (Coumadin)



Phenprocoumon (Marcumar®)

Figure 2: Chemical structure of coumarins from *Pelargonium sidoides* and anticoagulants of coumarin type (Koch and Biber, 2007)

In view of these results, it seems unlikely that an increased bleeding tendency can arise in patients treated with EPs 7630 (Loew and Koch, 2008; Brendler and van Wyk, 2008).

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

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. No evidence for toxicity was observed in the dosages and concentrations used. Full details are not available.

3.3.1. Single dose toxicity

Constituents of Pelargonium radix

Rajalakshmi *et al.* (2001) studied the acute toxicity of gallic acid in Swiss albino mice. Oral administration of 5 g/kg body weight to both male and female animals did not produce any signs of toxicity or mortality. Therefore, this value is considered the no-observed-adverse-effect level (NOAEL) of gallic acid in mice.

3.3.2. Repeat dose toxicity

Herbal preparations from Pelargonium radix

One study conducted with the extract EPs 7630 in toxicological studies in rats and dogs revealed a NOEL >750 mg/kg body weight of EPs 7630. According to the authors, this value represents a safety factor of more than 100-fold for humans (Loew and Koch, 2008).

Constituents of Pelargonium radix

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 (Rajalakshmi *et al.*, 2001).

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 haematological examinations suggested development of anaemia, of probably hemolytic origin. However, the severity of the anaemia 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).

3.3.3. Genotoxicity

No data available for pelargonium root.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

Hepatotoxicity

Herbal preparations from Pelargonium radix

Koch (2006) examined the hepatotoxic effect of extracts from the roots of *Pelargonium sidoides*. 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 pre-treatment with EPs 7630 (0-50 µg/ml) for 24 hours.

The hepatotoxic risk can be considered only for specific compounds belonging to the 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.

Constituents of Pelargonium radix

Some investigations have examined the hepatic biochemical and morphological changes produced in the rats after 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. The different metabolism and excretion in humans can explain the low risk of coumarin-induced hepatotoxicity in humans (Lake, 1999).

3.3.8. Conclusions

Acute toxicity studies with by pelargonium preparations are scarce but do not show safety concerns.

Although some toxicological data exist for preparations or isolated compounds from pelargonium root, there are no complete data available for the preparations listed in the monograph.

In relation to the hepatotoxic risk observed for specific compounds belonging to the group of coumarins, these substances are structurally different from the 7-hydroxy-coumarins isolated from pelargonium root extracts which, according to scientific literature, do not have hepatotoxic properties.

Teratogenicity data on pelargonium are not available. Tests on genotoxicity, reproductive toxicity and carcinogenicity have not been performed for the preparations listed in the monograph.

3.4. Overall conclusions on non-clinical data

There are no studies available which support the proposed indication for Pelargonium root extracts. The reported pharmacological effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Although non-clinical information on the safety of pelargonium is scarce, the results of available data raise no safety concern.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.
Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

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

In line with published literature and studies, the abbreviation BSS is used throughout this Assessment report for the Bronchitis Severity Score/ Bronchitis-Specific Symptoms or also Bronchitis Severity Scale.

The BSS total score consists of the five symptoms coughing, sputum, pulmonary rales at auscultation, chest pain while coughing and dyspnoea, rated on a scale from 0 to 4 (not present, mild, moderate, severe and very severe) and leading to a maximum total score of 20 points.

The symptoms and findings assessed in the BSS were first described in 1996 by Haidvogl *et al*. and Dome and Schuster. Later on, Blochin *et al*. (1999) and Golovatiouk and Chuchalin (2002) used the full scale, but the term "BSS" was introduced in the scientific literature in 2003 by Matthys *et al.* and has since been used in many further publications (Lehrl *et al*., 2014). Bronchitis Severity Score Scale was later validated retrospectively and published by Matthys and Kamin (2013).

Although the marketing authorisation holder of EPs 7630 preparations provided some reports on unpublished clinical trials, the Committee decided not to take them into consideration because of the definition of the well-established use: "Being a derogation the well-established use provision must be interpreted strictly. The well-established medicinal use legal basis is to be used only in cases where all aspects of the safety and efficacy are demonstrated by reference to published scientific literature" (Notice to applicants Volume 2A Chapter 1, https://health.ec.europa.eu/system/files/2019-07/vol2a_chap1_en_0.pdf).

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 times 30 drops, was established only empirically as usual with phytotherapeutic preparations.

One dose-response study was performed with the solid dosage form to assess the Efficacy and tolerability of EPs 7630 tablets in patients with acute bronchitis (Matthys *et al*., 2010b, also published by Matthys *et al*., 2010a; Schulz, 2008a).

This dose-finding, randomised, placebo controlled, double-blind trial, was carried out from February to April 2006 at 16 centres in Ukraine 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. 405 adults (>18 years old) were included in the study.

Inclusion criteria:
The main criteria for inclusion were that the start 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 per day, an herbal drug preparation from the roots of Pelargonium sidoides (1:8–10), dried, extraction solvent: ethanol 11% (w/w). Following a screening visit, the patients took their assigned treatment 30 minutes before meals 3 times daily for 7-day double-blind treatment period including three visits (days 0, 3–5, and 7).

Exclusion criteria:
*I*ndication for antibiotic treatment; suspected pneumonia; treatment with antibiotics, ACE-inhibitors, beta-blockers, bronchodilators, or glucocorticoids within 4 weeks prior to study inclusion; treatment with analgesics, secretolytics, mucolytics, or antitussives during the 7 days prior to study inclusion; allergic bronchial asthma; concomitant bacterial disease or diseases of the upper respiratory tract (e.g., influenza, sinusitis, tonsillitis); tendency to bleed; severe heart, renal, or liver diseases and/or immunosuppression.

Concomitant medication:
If patients had a fever (≥39° C), they were allowed to take 500 mg paracetamol tablets, but no more than three tablets daily.

Criteria for Evaluation

I. *Primary efficacy* variable:
The change in the total score of bronchitis-specific symptoms (BSS) from day 0 to day 7 was rated by the investigator.

II. *Secondary efficacy* variables were, among others:
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;

- Treatment outcome 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');
- Onset of effect;
- Change of individual symptoms of the BSS total score;

- Duration of activity limitation and inability to work assessed by diary entry (from day 0 to day 7) maximum inability duration of 8 days);
- Patient's satisfaction with treatment using the Integrative Medicine Patient Satisfaction Scales (IMPSS; 5-point verbal rating scale: 1=very satisfied, 2=satisfied, 3=neutral, 4=dissatisfied, 5=very dissatisfied).

III. *Safety*

Tolerability was assessed by surveillance of adverse events (AEs), laboratory safety parameters.

Statistical analysis

The study was planned and performed with an adaptive interim analysis. The intra-individual differences of the BSS total score between baseline (day 0) and day 7 were taken as the primary outcome variable for confirmatory treatment group comparisons of efficacy. The three single null-hypotheses comparing the active dose levels to placebo were tested with an analysis of covariance (ANCOVA) with the factors 'treatment group' and 'centre' and the covariate 'baseline value of the BSS total score'. The sample size was planned in order to assure a power of at least 80% to reject the hypotheses of no additional treatment effect of the EPs 7630 groups compared to the placebo group in the pair-wise comparisons already in the interim analysis, if treatment effects of Δ=1.5 points and standard deviations of 3.5 points are assumed.

Regarding the secondary efficacy variables, descriptive statistical methods were used for the comparison of treatment groups and the resulting p-values were interpreted accordingly. After baseline, missing values for efficacy variables were replaced applying the last observation carried forward (LOCF) method unless otherwise stated.

Results

- *Efficacy*

Primary outcome measure:

BSS score: Between day 0 and day 7, the mean BSS score decreased by 2.7±2.3 (mean ± standard deviation) for placebo, 4.3±1.9 for 30 mg group, 6.1±2.1 for 60 mg group and 6.3±2.0 points for 90 mg group, respectively. The tests of the global and intersection hypotheses within the closed test procedure, including the pair-wise comparisons of each active treatment group to placebo revealed statistically significant differences with respect to the decrease in BSS score between day 0 and day 7 for all EPs 7630 groups ($p < 0.0001$, in each case, one-sided.

A statistically significant difference in the BSS total score for all EPs 7630 groups compared to placebo was observed on day 3–5 and increased further to day 7 in a dose-dependent manner.

An increase in efficacy in the 60 mg EPs 7630 group compared to the 30 mg EPs 7630 group can be seen. Exploratory analysis revealed a statistically significant superiority of the 60 mg EPs 7630 group in the primary efficacy variable. No additional efficacy was seen for 90 mg.

Secondary outcome measures

Response criteria:

Response rates were higher in all EPs 7630 groups compared to placebo.

- Criterion 1 (BSS total score <3 points on day 7) was fulfilled by 5.9% of placebo patients and 24.5, 57.4 and 55.0% of patients receiving 30, 60 and 90 mg EPs 7630, respectively.
- Criterion 2 (decrease in BSS total score of at least 7 points from day 0 to day 7) was achieved by 6.9% of placebo patients and 14.7, 43.6 and 46.0% of patients in the 30 mg, 60 mg and 90 mg groups, respectively.

- Criterion 3 (combination of criteria 1 and 2), the response rate was also lower for placebo (2.9%) than for EPs 7630 (6.9, 33.7 and 31.0% in the 30 mg, 60 mg and the 90-mg groups, respectively).
  The difference in response rate between placebo and 30 mg EPs 7630 was statistically significant only for criterion 1 (p=0.0002). Statistically significant differences between the EPs 60 and 90 mg groups and placebo were observed for all three response criteria (p=0.0001, in each case).

Individual bronchitis specific symptoms
The mean decrease in the five individual bronchitis specific symptoms from day 0 to day 7 was markedly more pronounced in the active treatment groups compared to placebo. The reduction in intensity of symptoms was almost the same in the 60 and 90 mg groups. The reduction in the intensity of each symptom increased in a statistically significant way with the EPs 7630 dose (p<0.0001, in each case). Pair-wise comparison with placebo showed that the effect of EPs 7630 on the improvement of 'coughing' and 'pulmonary rales on auscultation' from day 0 to day 7 was statistically significant (p<0.0001, in each case).
For 'sputum', 'chest pain while coughing' and 'dyspnoea', statistically significant differences were observed between placebo and the 60 and 90 mg groups (p<0.0001, in each case, two-sided t-test).

Investigator's assessment
The results of the investigator's assessment concerning treatment outcome showed a markedly higher rate and degree of improvement in the active treatment groups compared with placebo. A better IMOS was calculated for all active treatment groups from both the investigator's and patient's assessments (p<0.0001 for all pair-wise comparisons with placebo). The rates for the combined categories 'completely recovered'/'major improvement' were 10.8% for placebo, 39.2% for EPs 7630 30 mg, 69.3% for EPs 7630 60 mg and 77.0% for EPs 7630 90 mg.
The majority of patients in the placebo group reported no treatment effect at all (42.2%) or onset of effects not before day 5–7 (38.2%), whereas more than 50% of patients in the EPs 60 mg (59.4%) and 90 mg groups (67.0%) reported an onset of effect between day 1 and 4.
Between day 0 and day 7, the number of patients unable to work dropped from 92.2, 87.3, 93.1 and 89.0% to 52.0, 21.6, 12.9 and 6.0% of patients in the placebo, EPs 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.

Evaluation of patients' satisfaction with treatment (IMPSS) showed comparable results (p<0.0001). Patients were more often satisfied or very satisfied with EPs 7630 (55.9% for EPs 7630 30 mg, 86.2% for EPs 7630 60 mg, 84.0% for EPs 7630 90 mg) than with placebo (23.5%).

Exploratory analyses revealed a statistically significant superiority of the 60 mg EPs 7630 group compared to the 30 mg EPs 7630 group in most of the secondary efficacy variables.

- *Safety*

Almost all patients (97.8%) took the trial medication as prescribed with no relevant difference in compliance between the treatment groups throughout the study. A total of 92 mild or moderate adverse events were observed in 18.5% of patients. The organ class with the largest number of patients affected by adverse events was the System Organ Class 'gastrointestinal disorders' 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). None of the adverse events was classified as serious. The occurrence of gastrointestinal disturbances increased dose-dependently.
As a main conclusion of the study, although analyses of the dose–response curve consistently indicate an increasing efficacy of EPs 7630 tablets with increasing daily doses, 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.

Assessor's comment:
This study is only an exploratory, dose finding study. Although the difference between the decrease of the BSS 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 article does not mention how big a difference in the primary outcome criterion was predefined as clinically relevant difference. For the deficiencies regarding the decrease in the BSS, see assessment of Golovatiouk and Chucalin (2002).
Moreover, the study was performed in 16 centres in a non-EU country (Ukraine). Since from another study (see Matthys et al., 2003) it is known, that this could lead to different outcomes, the requirements of ICH E5 (R1) should have been addressed to allow an assessment for the EU.
In addition, the articles provided very few numerical data; most of the results are presented only by figures, which show only the tendencies. For example, it would be good to see how many percent of patients was free of symptoms by the end of treatment in the different treatment groups in this self-limiting disease; e.g. whether there was a difference between the 16 centres considering the efficacy
Conclusion: Although - according to the publications – some effects were seen in secondary parameters the HMPC concluded that those results could not be taken as proof on clinical efficacy of the preparation from the roots of Pelargonium sidoides (1:8–10), dried, extraction solvent: ethanol 11% (w/w). Clinically relevant effects should have been presented for the primary endpoint.

4.2.2. Clinical studies (case studies and clinical trials)

4.2.1.1 Acute bronchitis

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

The study by Golovatiouk and Chucalin (2002) (later published by Chuchalin *et al*. (2005) and Schulz (2006, 2007) as well) was a multicentre, prospective, randomized, double-blind, placebo-controlled study of adaptive-sequential design and was performed in 6 centres in Moscow (Russia) from April 2000 to March 2001. Sixty-four patients were treated with EPs 7630 solution and sixty patients with placebo.

Inclusion criteria were: age from 18 years on, acute bronchitis, first symptoms before ≤48 hours, and total score of typical bronchitis symptoms ≥5 points.

Exclusion criteria were: patients with compelling indication for an antibiotic treatment, or who were treated with antibiotics within the past 4 weeks previous to inclusion into the study, patients with allergic bronchial asthma, with increased bleeding tendency, severe cardiac, renal or hepatic diseases and/or immune suppression.

The primary target variable for evaluating the efficacy of EPs as compared to placebo was the change in total score of the 5 typical bronchitis symptoms on day 7. A 5-level rating scale-bronchitis severity score (BSS)-was used, which consists of the five symptoms coughing, sputum, pulmonary rales at auscultation, chest pain while coughing and dyspnoea, rated on a scale from 0 to 4 (not present, mild, moderate, severe and very severe) and leading to a maximum total score of 20 points.

Secondary target variables were: single scores of the typical bronchitis symptoms and further symptoms, treatment success on the base of the IMOS scale („Integrative Medicine Outcomes Scale"

(IMOS: symptom free, clearly improved, slightly to moderately improved, unchanged, deteriorated), onset of action of trial medication, consumption of paracetamol, health condition of patient on the base of questionnaires on health-related quality of life (SF-12, EQ-5D), satisfaction of patient with treatment (IMPSS) and tolerability of medication including occurrence of adverse events. Laboratory tests including leukocytes, erythrocyte sedimentation rate, gamma-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, Quick test, and partial thromboplastin time (PTT) were performed as well.

The investigational medication was administered in bottles of 50 ml containing either EPs 7630 (100 g finished product contain 80 g EPs 7630; additional ingredient of the finished product: 20 g glycerol 85%) or placebo to a formulation of EPs 7630 with regard to colour, smell, and taste as well as viscosity. All patients received the same prescribed dose of 30 drops three times per day (to be taken 30 minutes before or after meals over a maximum period of 7 days. Concomitant medications able to influence the study result (e.g. antibiotics) were not allowed during the trial duration.

The study had a confirmatory design, as the aim was to prove the superiority of EPs against placebo on the base of the primary target variable. The study was scheduled according to a five level group-sequential test plan with case adjustments after four interim assessments. All 124/124 randomized patients were included in the intention-to-treat analysis (ITT); all missing data were completed by means of the LOCF method (last observation carried forward). The corresponding results of the per-protocol analysis (n=121) produced only slight differences as against the ITT analysis; thus, only the results of the ITT analysis are being reported in the following.

Out of the 124 patients of the ITT analysis, 37 (30%) were men and 87 (70%) women. The average age was 36 years. There were no relevant differences between the verum and the placebo group with respect to the demographic data. Regular intake of the trial medication was reported for a total of 122 (98.4%) patients.

By day seven, 3 out of 64 patients in the EPs 7630 group (Lack of efficacy, n=1; Free of symptoms, n=1; Not allowed concomitant medication, n=1) and 4 out of 60 patients in the placebo group had dropped out (Lack of efficacy, n=2; Violation against selection criteria, n=2) (Chuchalin *et al*., 2005).

The main results were: The mean total score of the 5 typical bronchitis symptoms was 9.0±2.2 points on day 0 in the EPs group and 9.1±2.2 points in the placebo group. Over the course of the treatment, the total score decreased under EPs by 7.2±3.1 points and under placebo by 4.9±2.7 points (*P* <0.0001). The 95% RCI for the difference of effects between the two treatment groups (EPs 7630 minus placebo) was calculated as (1.2, 3.6) showing a highly significant superiority of EPs 7630 compared with placebo on day seven. This superiority of EPs 7630 was noticeable at the first follow-up contact (days 3-5) already (BSS: 4.4±2.2 points under EPs 7630, 6.2±2.5 points under placebo, *p* <0.0001) (Chuchalin *et al*., 2005). Relevant differences between the 6 trial centres were not observed.

Regarding secondary efficacy, the response criteria based on BSS on day seven showed: A BSS of less than five points was observed in 61 of 64 patients (95.3%) with EPs 7630 compared with 35 of 60 patients (58.3%) with placebo (p<0.0001). A decrease of BSS of at least five points compared with baseline was seen in 58 of 64 patients (90.6%) treated with EPs 7630 and 31 of 60 patients (51.7%) treated with placebo (p<0.0001). Rapid recovery, defined as fulfilment of both of outcomes above, was observed in 58 of 64 patients (90.6%) with EPs 7630 and 25 of 60 patients (41.7%) with placebo (p<0.0001).

Individual symptoms of BSS on day seven: For each of the five individual symptoms, the rate of complete recovery on day seven was considerably higher in the EPs 7630 group.

On day seven, rales/rhonchi had disappeared in 55 of 60 patients (91.7%) under EPs 7630 and in 29 of 59 patients (49.2%) under placebo (p<.0001), and chest pain during coughing had disappeared in

55 of 58 patients (94.8%) of the EPs 7630 group and 29 of 52 patients (55.8%) of the placebo group (*p< 0.0001*). Among the five symptoms, cough was the symptom with the highest baseline scores and the slowest recovery in both groups. In the EPs 7630 group, cough disappeared in 20 of 64 patients (31.3%) compared with three of 60 patients (5.0%) in the placebo group (*p*< 0.0001) (Golovatiuk and Chuchalin, 2002).

For the Treatment Outcome, the following values were obtained for the evaluation of the therapeutic success by the physician according to the IMOS scale at the end of the treatment (numbers verum vs. placebo in % in each case): freedom from symptoms 28 vs. 2; clearly improved 56 vs. 28; slightly/moderately improved 11 vs. 60; unchanged 2 vs. 10; deteriorated 2 vs. 0. The corresponding evaluations by the patients showed similarly positive results.

Regarding the onset of action, the EPs vs. placebo patients gave the following outcomes: 3% vs. 0% after a few hours, 22% vs. 10% after 1-2 days, 44% vs. 23% after 3-4 days, 27% vs. 43% after 5-6 days and 3% vs. 23% after 7-10 days.

Health related quality of life improved more in patients in the EPs 7630 group compared with placebo-treated patients. Group differences were most marked in pursuance of "usual activities" (78.2% vs 34.8%, respectively), followed by "mobility" (85.0% vs 54.1%, respectively), "anxiety/depression" (78.0% vs 48.8%, respectively), and "pain/discomfort" (78.0% vs 47.3%, respectively) and were still found in "self-care" (90.5% vs 75.0%, respectively) (Chuchalin *et al*., 2005).

The tolerability assessments by the investigators and the patients on day seven were similar. A very good or good tolerability was reported by 98.4% of the patients in the EPs 7630 group and by 96.7% of the patients in the placebo group.

A total of 25 of 124 patients (20.2%) experienced at least one AE during the trial: 15 of 64 patients (23.4%) in the EPs 7630 group and 10 of 60 patients (16.7%) in the placebo group, with intensities ranging from mild to moderate. Adverse events for which a relation with the trial medication could not be excluded by the investigator, i.e. which were judged as possible or probable, were documented for 10/64 (15.6%) in the EPs group and 8/60 (13.3%) in the placebo group. Compared to the placebo group, more patients under EPs complained about gastrointestinal disorders. All adverse events were assessed as nonserious. Regarding the coagulation parameters Quick and PTT, no differences between the two treatment groups were observed (Chuchalin *et al*., 2005).

Assessor's comment:
The study was performed in a non-EU country in 6 centres in Moscow (Russia), the requirements of ICH E5 (R1) should have been addressed to allow an assessment for the EU.
In this publication, also it was not pre-defined how big a difference between the effects of the treatment compared with placebo would be expected as clinically relevant effect considering the primary outcome criterion. Therefore, the results of the study cannot be assessed.
A general agreement on this requirement for the BSS cannot be found in the literature and HMPC did not discuss this issue when the validation of the BSS was evaluated in 2013. The authors of the study presented the change found in the study as proof of efficacy. However, since the clinically relevant difference was not predefined and justified, this assessment cannot be followed (see also ICH E8 and E9).

During the assessment of clinical studies with EPs 7630 the HMPC decided that in this self-limiting disease one grade of better improvement in the treatment group compared with the placebo group is considered clinically relevant.
There are five items: cough, sputum, rales/rhonchi, and chest pain during coughing and dyspnoea. Each item can receive 0-4 points according to the severity of symptoms. The severity of the disease is mild if the score is 0-5, moderate if it is 6-10, and severe if it is 11-15 and so on. If sputum is

disregarded, which existed only for some patients, 4 points of decrease can be considered as clinically relevant improvement.
One grade of better improvement in the active treatment group than in the placebo group – at least 4 points of difference-could be considered as clinically relevant difference. However, the definition of the clinical relevance should be determined for each therapeutic field, for every clinical study individually already before the start of the study, under consideration of the circumstances of the specific patient population.

Although the difference between the decrease in the BSS score in the EPs 7630 (7.2±3.1) group and in the placebo (4.9±2.7) group is statistically significant ($p < 0.0001$), it is not considered as clinically relevant, since the difference in the improvement (degree of BSS decline) between the two treatment groups is only 7.2-4.9= 2.3 (primary endpoint).
Conclusion: Although-according to the publications–some effects were seen in secondary parameters the HMPC concluded that those results could not be taken as proof on clinical efficacy of the liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m). Clinically relevant effects should have been presented for the primary endpoint.

Another randomized, double-blind, placebo-controlled trial using a multi-stage adaptive design was performed in 468 adult patients with acute bronchitis (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 (Matthys *et al*., 2003). Patients, who met the following criteria, were suitable for the trial: age >18 years, acute bronchitis, and duration of complaints (≤48 hours) and Bronchitis Severity Score (BSS) ≥5 points. The main exclusion criteria were an indication for antibiotic treatment or treatment with antibiotics during the period of 4-weeks prior to enrolment in the trial, allergic bronchial asthma, tendency to bleed, severe heart, renal or liver disease, immunosuppression, known or supposed hypersensitivity to trial medication. Following enrolment (Day 0), control examinations occurred on Day 3-5 and Day 7.

The investigational medication was administered in bottles of 50 ml containing either EPs 7630 (100 g finished product contain: 80 g EPs 7630, a aqueous ethanolic extract [11% (m/m)] of the roots of *Pelargonium sidoides* corresponding to 8 g plant material; additional ingredient of the finished product: 20 g glycerol 85%) or placebo. Placebo was matched to a formulation of EPs 7630 with regard to colour, smell and taste as well as viscosity. The patients were instructed to take 30 drops three times daily (4.5 ml per day) at 30 min before or after the meals starting at day 0 and continuing until day 7. In case of fever (>39°C), paracetamol tablets 500 mg were allowed.

Criteria for withdrawals were: no decrease of BSS compared to baseline (non-responder), complete recovery, intake of prohibited medications (e.g. antibiotics), occurrence of adverse events or suspected lack of compliance.

The primary outcome criterion for assessing the efficacy of EPs 7630 compared to placebo was the change of BSS on Day 7. BSS scores 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 5-point rating scale ranging from 0 to 4 (0: absent; 1: mild; 2: moderate; 3: severe; 4: very severe).

Secondary outcome criteria were: Prospective defined response criteria based on BSS (A: BSS < 3 points; B: decrease of BSS >7 points; C: A+B), treatment outcome according to the Integrative Medicine Outcomes Scale (IMOS), onset of treatment effect, consumption of paracetamol, change of individual symptoms of BSS and further symptoms, patients' health status using the health-related quality of life questionnaires (SF-12 Health Survey, EQ-5D), questions about the complaints and satisfaction with treatment using the Integrative Medicine Patient Satisfaction Scale (IMPSS).

The safety of treatment was assessed with respect to frequency, nature and severity of adverse events (AEs), to tolerability assessed by investigators and by patients using a verbal 4-point rating scale, and to the results of laboratory tests (leukocytes, erythrocyte sedimentation test, g-GT, GOT, GPT, Quick's test, PTT). Following enrolment (day 0), control examinations occurred on day 3–5 and day 7.

Treatment outcome and tolerability were assessed separately by the patient and the investigator. On day 7 or at premature withdrawal of the patient, there was a final assessment including laboratory tests and sputum analysis. In addition, the patient was asked with regard to the time until start of treatment effect and satisfaction with treatment.

Statistical analysis: All interim and final confirmatory statistical analyses of the primary outcome variable were based on all available data according to the intention-to-treat principle. The last observation carry forward (LOCF) procedure was applied in case of premature withdrawal from the trial. All confirmatory comparisons of the two treatments were carried out as planned, namely as 2-factorial analysis of covariance on the primary outcome variable with the two factors treatment group and site, and with the baseline value as a covariate. Results are displayed as means ± standard deviation. For confirmatory analysis, 95% Confidence Intervals (CIs) were calculated.

In relation to the results, among the 468 patients in the ITT data set, 299 patients (63.9%) were female and 169 patients (36.1%) were male. The predominance of females was slightly higher in the placebo group (EPs 7630: 139 patients [59.7%]; placebo: 160 patients [68.1%]). 2 among 476 patients were excluded because they did not take any investigational medication and 6/476 were excluded for reasons of non-compliance with Good Clinical Practice.

At baseline, BSS was similar in both treatment groups (8.4±2.2 points in the EPs 7630 group, 8.0±2.0 points in the placebo group). On day 7 (LOCF), BSS decreased by 5.9±2.9 points under EPs 7630 and by 3.2±4.1 points under placebo ($p< 0.0001$). The 95% CI for the difference of effects between the two treatment groups (EPs 7630 minus placebo) was calculated as [−3.359; −2.060] showing a highly significant superiority of EPs 7630 compared to placebo on day 7. This superiority of EPs 7630 was noticeable at the first follow-up contact (day 3–5) already (BSS: 4.8±2.3 points under EPs 7630, 6.2±3.0 points under placebo ($p<0.0001$).

In addition, it was also observed in patients with more severe bronchitis defined as BSS >8 points at baseline (n=279, decrease of BSS: 6.8±2.7 points under EPs 7630, 4.5±4.2 points under placebo, ($p<0.0001$).

Response criteria based on BSS on day 7 A BSS of less than 3 points (response criterion A) was observed in 150/233 patients (64.4%) under EPs 7630 compared to 89/235 patients (37.9%) under placebo (Fig. 16, $p<0.0001$). A decrease of BSS of at least 7 points compared to baseline (response criterion B) was seen in 101/233 patients (43.3%) treated with EPs 7630, and 54/235 patients (23.0%) treated with placebo ($p<0.0001$). Rapid recovery, defined as fulfilment of response criteria C (C = A + B), was observed in 80/233 patients (34.3%) under EPs 7630, and 48/235 patients (20.4%) under placebo ($p<0.0001$).

In relation to the Individual symptoms of BSS on day 7, high recovery rates for EPs 7630 were observed for the symptoms rales/rhonchi, chest pain during coughing and dyspnoea. For example, on day 7, rales/rhonchi had disappeared in 165/214 patients (77.1%) under EPs 7630 and in 95/214 patients (44.4%) under placebo (p<0.0001), and chest pain during coughing had disappeared in 174/208 patients (83.7%) of the EPs 7630 group and 103/214 patients (48.1%) of the placebo group (p<0.0001). The recovery rates for cough and sputum were similar in the EPs 7630 and placebo group, but the rates for improvement of these symptoms were clearly higher in the EPs 7630 group. In the EPs 7630 group, cough disappeared or improved in 207/232 patients (89.2%) compared to 133/235 patients (56.6%) in the placebo group (p<0.0001), and the symptom sputum disappeared or improved

in 122/185 patients (66.0%) under EPs 7630 compared to only 83/174 patients (47.7%) under placebo (p<0.0002).

At baseline, 67% of the patients in both groups were unable to work. On day 7, working inability decreased to 16% in the EPs 7630 group compared to 43% in the placebo group (p<0.0001). In addition, the duration of illness was significantly shorter for patients treated with EPs 7630 compared to placebo (p<0.001). EPs 7630-treated patients were able to return to work nearly two days earlier than placebo-treated patients (4.7±3.7 days vs. 6.3±4.5 days, p<0.0001).

On average, all subscales of the EQ-5D health questionnaire showed a positive tendency in favour of the EPs 7630 group at the end of the trial. For example, EQ-VAS increased by 29 units in the EPs 7630 group and by 21 units in the placebo group (p<0.0001). With regard to the onset of treatment effect, patients noticed an effect earlier under EPs 7630 than under placebo. Within the first four days, onset of treatment effect was recognised in 53.6% of patients under EPs 7630 compared to 36.2% of patients under placebo, only (p<0.0002).

According to the entries of the patient diaries, 174/233 patients (74.7%) in the EPs 7630 group and 99/235 patients (42.1%) in the placebo group were satisfied with their treatment (p<0.0001), whereas only 9/233 patients (3.9%) in the EPs 7630 group, but 63/235 patients (26.8%) in the placebo group were dissatisfied (p<0.0001).

The tolerability assessments by the investigators and the patients were similar. A very good or good tolerability was reported by 96.1% of the patients in the EPs 7630 group and by 88.1% of the patients in the placebo group. The mean values of all laboratory parameters did not change during the trial, neither for patients under EPs 7630 nor for patients under placebo.

Twenty six adverse events with probable, possible or improbable relation to the investigational medication were described for the patients treated with EPs 7630 and 11 for the patients treated with placebo. The organ system most frequently affected by adverse events were gastrointestinal disorders, nervous system disorders, respiratory/thoracic and mediastinal disorders, and ear and labyrinth disorders.

Assessor's comment:
In comparison with the other two placebo controlled studies performed with the liquid extract, here again only small differences can be seen between the effect of Pelargonium sidoides compared with placebo: 5.9±2.9 vs. 3.2±4.1 (p<0.0001). Difference between verum vs. placebo is 5.9-3.2=2.7. For the deficiencies regarding the decrease in the BSS see assessment of Golovatiouk and Chucalin (2002). In addition, there are a large number of withdrawals in this study, which is not emphasized by the authors since the numbers can be read only from the Figure (see Figure 14 above): Seventeen patients in EPs 7630 group (7.2%) and 93 patients in the placebo group (38.9%) dropped out from the trial on day 3-5. From these withdrawals nine in the verum group (3.8%) and 87 in the placebo group (36.4%) were due to lack of efficacy. The article does not explain this large number of withdrawals.
There is no data in this article whether there was a difference between the different investigation sites (36 centres) or not. Another article about the validity of BSS score (Lehrl et al., 2014) subdivided this study into two sections because one part was performed in Germany with German doctors and patients and the other in Ukraine with Ukrainian doctors and patients. The reasoning for this separation was the following: "Possibly the different backgrounds of history and native language could exert different influences on the results."
Although the authors of this study also highlighted that for all individual symptoms, recovery and/or improvement rates were higher in the EPs 7630-treated patients compared to the placebo-treated, the recovery rates for cough and sputum were similar (19.4% versus 13.6% and 35.1% versus 32.2%) in the EPs 7630 and in the placebo group. Although EPs 7630-treated patients were able to return to

work nearly two days earlier than placebo-treated patients (4.7±3.7 days vs. 6.3±4.5 days, p <0.0001), this good result is questionable due to the high number of drop-outs (37.4%) from the placebo group.
Conclusion: Although -according to the publications– some effects were seen in secondary parameters the HMPC concluded that these results cannot be taken as proof on clinical efficacy of the liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m). Clinically relevant effects should have been presented for the primary endpoint in which only small differences have been seen between the effects of the treatment compared to placebo.
Furthermore, the results of this study cannot be considered because there was a big number of withdrawals in the placebo group (38.9%), which can distort these results. According to another article there was also a difference between the investigation sites (Germany and Ukraine).

The randomised, double-blind, placebo-controlled, multicentre study by Matthys and Heger (2007a) (published later by Matthys and Funk (2008) as well) aimed to assess the efficacy and safety of the preparation EPs 7630 in the treatment of acute bronchitis in adults outside the very restricted indication for an antibiotic therapy. The study was conducted in Moscow, Russian Federation between October, 2000 and March, 2002. Patients were included in a total of six trial sites.

217 patients aged between 18 and 66 years with acute bronchitis were included, fulfilling the following criteria for inclusion: the onset of symptoms of acute bronchitis had to be ≤48 hours prior to inclusion the study and total score of bronchitis-specific symptoms (BSS) had to be ≥5 points at screening.

Exclusion criteria were indication for antibiotic therapy, treatment with antibiotics 4 weeks prior to enrolment, allergic bronchial asthma, tendency to bleed, severe heart, renal, or liver diseases, immunosuppression, known or supposed hypersensitivity to investigational medication, concomitant medication that might impair the trial results (e.g., antibiotics).

Among the 217 patients who participated, 108 were given 30 drops of EPs 7630 solution three times daily and 109 patients received 30 drops of matched placebo three times daily for a period of 7 days.

Following enrolment, patients were assessed at baseline (Day 0) during treatment at Day 3 to Day 5 and at the end of the active treatment period (Day 7). The patient diary had daily entries.

Ten of overall 13 withdrawals from the placebo group were due to lack of efficacy whereas none of overall 6 withdrawals in the active treatment group were due to lack of efficacy.

The patient's demographics and baseline characteristics are fairly well distributed between the two groups. Slight differences between the groups for females and previous medical history appear to be within the expected range. There were slightly more females in the placebo group (86 [78.9%]) than in the treatment group (78 [72.2%]). There were slightly more former smokers in the treatment group (16 [14.8%]) than in the placebo group (12 [11.0%]).

The primary outcome criterion was the change in BSS from day 0 to day 7 of treatment.

Secondary efficacy endpoints were assessed with categorisation of the symptoms fatigue, headache, hoarseness, painful limbs, and fever on a categorised ordered self-reporting instrument with 4 grades (not present, mild, moderate, severe) and all individual items of the BSS. The proportion of patients requiring bed rest and being able to work was documented as well as the consumption of paracetamol tablets for fever >39 'C. Additional health-related quality of life questionnaires (SF-12 Health Survey, EQ-5 D) were used.

Statistical analysis. The trial was planned according to a group sequential design with the option of early stopping or continuation with sample size adjustment after the interim analysis.

Primary outcome measure: At day 0, BSS was 8.9±1.6 points for the treatment group and 8.4±1.8 points for the placebo group. At the first visit (day 3-5), BSS decreased to 4.2±2.0 points in the treatment group and 5.9±2.5 points in the placebo group. After 7 days of treatment, the BSS decreased by 7.6±2.2 points in the EPs 7630 group and by 5.3±3.2 points in the placebo group. The 95% confidence interval for the difference between the effects was calculated as 1.6-3.1, showing highly significant superiority for the EPs 7630 treatment ($p<0.0001$).

For all secondary efficacy variables, marked effects in favour of the EPs 7630 group have been seen. Treatment response rate-amongst others-defined as BSS≤3 points at Day 7 and a BSS decrease of ≥7 points-was different in the two groups. Eighty patients (74.1%) responded to treatment in the EPs 7630 groups compared with 29 patients (26.6%) in the placebo group (Matthys and Funk, 2008). 45.4% of the patients on active treatment were assessed by physician as having experienced complete recovery at day 7, in comparison with 6.4% of patients on placebo. For all single components of BSS and the additional five symptoms associated with general infection, a clear advantage of EPs 7630 -as shown by the number of patients reporting complete remission after seven days of treatment- was reported.

Patients in the EPs 7630 treatment group were less bound to bed and sooner able to work than patients in the placebo group. At Day 3-5, 6.5% of patients in the EPs 7630 group were bound to bed compared with 14% in the placebo group. Moreover, at the final visit, only 18.4% of patients receiving EPs 7630 treatment were unable to work compared with 33.3% of patients receiving placebo.

During the study, no serious adverse events were recorded. A total of 21.7% (47/217) patients experienced at least one AE: 21.3% (23/108) patients in the EPs 7630 group and 22.0% (24/109) in the placebo group. There was no relevant difference in the distribution of the adverse events over the different treatment groups.

Assessor's comment:
This study also shows the same deficiencies. It was conducted in a non-EU country (in Moscow, Russian Federation). There is no predefinition of a clinically relevant effect. The difference between the effect of the treatment with Pelargonium sidoides compared to placebo is again statistically significant: - 2.3 (7.6±2.2 points vs. 5.3±3.2 points, p<0.0001) but not clinically relevant, although some clinically relevant effects can be seen in secondary target variables. For the deficiencies regarding the decrease in the BSS see assessment of Golovatiouk and Chucalin (2002).
In this study, the number of drop-outs was also higher than in the placebo group: Ten of overall 13 withdrawals from the placebo group (12%) were due to lack of efficacy, whereas none of overall six withdrawals in the active treatment group were due to lack of efficacy.
Conclusion: The results of this clinical trial are not acceptable. Although -according to the publications– some effects were seen in secondary parameters, the HMPC concluded that these results cannot be taken as proof for clinical efficacy of the liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m). Clinically relevant effects should have been presented for the primary endpoint in which only a small difference has be seen between the effects of the treatment compared to placebo.

Apart from the above cited randomized clinical trials, other studies have been conducted with pelargonium preparations in the same therapeutic area.

The study by Matthys *et al*. (2007) was 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. 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%. 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 adverse events were classified as "gastrointestinal disorders".

The efficacy of EPs 7630 was investigated by Matthys and Heger (2007b) in another 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. The remission rate of individual symptoms was over 70% (Table 9.). Seventy eight per cent of the patients were satisfied with the treatment at the final visit. Eighteen adverse events were documented; eleven cases were adverse 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).

Two open studies have been conducted with pelargonium preparations on acute sinusitis.

In the multicentre, prospective, open study by Schapowal and Heger (2007), the efficacy and change in symptoms in 361 patients (aged 1-94 years) with acute sinusitis and acute exacerbation of chronic sinusitis following administration of EPs 7630 was assessed. Adult patients suffering from acute sinusitis received 30 drops every hour up to 12 times on day 1 and 2 and 3 times 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 times 20 drops daily on day 3-28. Patients with exacerbation of chronic sinusitis received prophylactic therapy: 2 times 30 drops for adults or 2 times 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. 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 favourable 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).

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 times 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 10.). 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 out of 103 patients experienced adverse events: 2 out of 52 patients (3.8%) in the EPs 7630 and one out of 51 patients (2%) in the placebo group. None of these events was classified as serious. A causal relationship to the study drug could not be excluded in one treated patient (mild epistaxis).

Assessor's comment:
Since the cold intensity score (CIS) is not a validated score, the results of this study are not evaluated.

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).

Table 4: Clinical studies on humans, in cough and cold

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score (e.g. Jadad score)**	**Comments on clinical relevance of results**
Acute bronchitis							
Golovatiouk and Chuchalin, 2002	DB,PC,R	Test product: EPs 7630 Oral liquid 30 drops, 3 times daily Duration: 7 days	n= 124 between 18-71years male: 23.4 vs. 36.7%	Acute bronchitis present (≤48 hours) BSS ≥5 points	BSS <5 points on day 7 decrease of BSS ≥5 both outcomes together 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	ITT yes CI 95% BSS	Not clinically relevant as the difference between treatment and placebo was not predefined and justified.
Matthys *et al*., 2003	DB,PC,R	Test product: EPs 7630 Oral liquid 30 drops, 3 times daily Duration: 7 days	n= 468 mean age: 41.1 vs.39.9 male: 40.3 vs. 46.9%	Acute bronchitis present (≤48 hours) BSS ≥5 points	BSS<3 points on day 7 decrease of BSS ≥7 both outcomes together Disappearance of individual symptoms on day 7: cough sputum	ITT yes CI 95% BSS	Not clinically relevant because small differences between groups, large number of

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score (e.g. Jadad score)	Comments on clinical relevance of results
					chest pain during cough rales/rhonchi dyspnoea working inability on day 7 able to work (days)		withdrawals, variability among centres included in the study.
Matthys and Heger, 2007a*, Matthys and Funk, 2008	DB,PC,R, MC	Test product: EPs 7630 Oral liquid 30 drops, 3 times daily Duration: 7 days	n= 217 mean age: 37.4 male: 24.4%	Acute bronchitis present (≤48 hours) BSS ≥5 points	BSS<3 points on day 7 and decrease of BSS ≥7 complete remission of individual symptoms on day 7: cough sputum rales/rhonchi chest pain during cough dyspnoea complete recovery assessed by the physician unable to work adverse events	CI 95% BSS	Not clinically relevant: lack of predefinition of a clinically relevant effect, large number of withdrawals, deficiencies in assessing the BSS decrease.

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score (e.g. Jadad score)**	**Comments on clinical relevance of results**
Matthys *et al*., 2007	MC, P, OO	EPs 7630 Oral liquid 30 drops, 3 times daily duration: 14 days	n= 2099 mean age: 34.5 41% male	productive cough for less than 6 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 adverse events	BSS	Not clinically relevant, although showed a high responder rate (68%).
Matthys and Heger, 2007b[#]	MC, P, OO	EPs 7630 Oral liquid 30 drops, 3 times daily duration: 7days	n= 205 mean age: 42 33.2% male	acute bronchitis (87.8%) or acute exacerbation of chronic bronchitis present (≤7 days)	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 adverse events	Not included	Not clinically relevant due to the lack of validated score, the uncontrolled use of other therapy measures, among others
Acute sinusitis							
Schapowal and Heger, 2007	MC, O	EPs 7630 adults: 30 drops every hours up to 12 times on day 1 and 2; 3 times 30	n=361 1-94 years mean age: 38±19	acute sinusitis or acute exacerbation of chronic sinusitis	1st reduction of total score of objective and subjective symptoms 2nd complete remission or improvement of	Sinusitis score	Not clinically relevant: lack of causal relationship

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score (e.g. Jadad score)	Comments on clinical relevance of results
		drops daily from day 3 Children (<12 years): 20 drops every hours up to 12 times on day 1 and 2; 3 times 20 drops daily from day 3 duration: Acute sinusitis: 28 days Exacerbation: 28 days+ 8 weeks prophylaxis–(2 times 30 drops daily for adults and 2 times 20 drops daily for children)			individual symptoms on day 28 2nd adverse events		with the study medication
Bachert *et al*., 2009*	DB,PC,R, MC	EPs 7630 60 drops, 3 times daily duration: maximum 22 days	n=103 mean age: 34.4 vs. 35.6 37% vs. 33% male	acute rhinosinusitis present at least 7 days SSS ≥12 points	1st reduction of SSS at day 7 2nd SSS<10 points on day 7 2nd complete remission (SSS=0 on day 21) 2nd adverse events	SSS	Not clinically relevant due to the small sample size
Common cold							
Lizogub *et al*.,	DB,PC,R,	EPs 7630	n=103	common cold	1st reduction of SSID at	CIS not	Not clinically

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score (e.g. Jadad score)**	**Comments on clinical relevance of results**
2007*	MC	30 drops, 3 times daily duration: maximum 10 days	mean age: 34.5 vs. 37.4 30.7% vs. 31.3% male	present 24-48 hours maximum symptoms score 40	day 5 2nd patients with clinically cure on day 10 2nd duration of inability to work (days) 2nd adverse events	validated	relevant due to the lack of validated score

Abbreviations: DB=double-blind, PC=placebo-controlled, R=randomised, MC= multicentre, * studies included in Cochrane Meta-analysis, # studies excluded in Cochrane Database

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

Several clinical trials have been performed with pelargonium preparations in children.

Kamin *et al*. (2010a) carried out a double-blind, placebo-controlled dose-finding study for EPs 7630 performed in children and adolescents to identify the appropriate dose of EPs 7630 and to demonstrate its efficacy, safety and tolerability in the 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 as a randomized, double-blind, placebo-controlled clinical dose-finding study with 4 parallel treatment groups. Individual duration of the study was 7 days. During this time, 3 visits were scheduled (day 0; days 3–5; day 7).

Male or female patients aged 6-18 years old suffering from acute bronchitis with symptoms starting ≤ 48 hours 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. Major exclusion criteria were: treatment with antibiotics, bronchodilators or glucocorticoids during the last 4 weeks, or with analgesics, secretolytics, mucolytics or antitussive during the last 7 days prior to study inclusion; indication for treatment with antibiotics; allergic asthma; tendency to bleed; severe heart, renal or liver diseases and/or immunosuppression, known hypersensitivity against *P. sidoides*; chronic obstructive pulmonary disease and pregnancy. Eligible patients were randomly allocated to one of four treatment groups in a balanced way (with a block size of four), according to a computer-generated randomization list.

Patients were given EPs 7630, a herbal drug preparation from the roots of *P. sidoides* (1:8–10), dried, extraction solvent: ethanol 11% (w/w), as EPs 7630 film-coated tablets [3 times 10 mg (=30 mg group), 3 times 20 mg (=60 mg group) or 3 times 30 mg per day (=90 mg group) EPs 7630] 30 min before or after a meal for 7 consecutive days, or a matched placebo for the same time period.

The primary efficacy variable was the change in the BSS total score from day 0 to day 7 rated by the investigator. The BSS total score consists of the five symptoms coughing, sputum production, pulmonary rales 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) to 4 (very severe) and leading to a maximum total score of 20 points.

Secondary efficacy variables were: treatment response according to three criteria (BSS total score of <3 on day 7, decrease in BSS total score of at least 7 points from day 0 to day 7 and BSS total score <3 on day 7 combined with a decrease in BSS total score of at least 7 points from day 0 to day 7), onset of effect, change of individual symptoms of the total score, change of general symptoms (e.g. 'absence of appetite', 'headache' and 'vomiting') and health status of patients using the questionnaires for health state of children (FGK, "Fragebogen zum Gesundheitszustand für Kinder").

Additional parameters were bed rest duration and ability to attend kindergarten, school or work. Treatment outcome was assessed by both the investigator and the patient using the Integrative Medicine Outcomes Scale (IMOS) consisting of a 5-point rating scale (1='complete recovery', 2='major improvement', 3='slight to moderate improvement', 4='no change' and 5='deterioration').

Satisfaction with treatment was assessed using the Integrative Medicine Patient Satisfaction Scale (IMPSS), a five-point scale comprising the ratings: 1='very satisfied', 2='satisfied', 3='undecided', 4='dissatisfied' and 5='very dissatisfied'.

Safety parameters were surveillance of AEs, laboratory safety parameters and vital parameters. Prior to unblinding, every AE was classified by the investigator in one of four categories according to the data available with regard to the possible causal relationship to the administration of the study medication (probable–possible–unlikely–no relationship).

Statistical methods. The study was planned and performed with an adaptive interim analysis. The primary outcome variable for confirmatory treatment group comparisons of efficacy was the intra-individual difference of the BSS total score between day 0 and day 7. The global null hypotheses (placebo vs. 30 mg vs. 60 mg vs. 90 mg and placebo vs. 30 mg vs. 60 mg; placebo vs. 30 mg vs. 90 mg; placebo vs. 60 mg vs. 90 mg) were tested using the Bartholomew test for unknown but common variances. The three single null hypotheses comparing each of the active dose levels with placebo were tested with an analysis of covariance (ANCOVA), with the factors 'treatment group' and 'centre' and the covariate 'baseline value of the total score of BSS'.

Regarding the secondary efficacy variables, descriptive statistical methods were used for the comparison of treatment groups and accordingly, the resulting p-values have to be interpreted in an exploratory manner. All statistics are based on the full analysis set according to the intention-to treat principle using the last observation carried forward method for missing values.

A total of 400 patients were included for screening and were subsequently randomized to receive 30, 60 or 90 mg EPs 7630 or matching placebo daily. All patients were included in the safety analysis. One patient in the 30 mg group could not be analysed for efficacy because of early dropout without any post-baseline measurement (withdrawal of consent). Thus, the full analysis set comprised 399 patients; 101 patients received placebo, 100 patients received 30 mg, 99 patients received 60 mg and 99 patients received 90 mg EPs 7630. The evaluation of baseline data revealed no noticeable differences between the treatment groups at baseline. Almost all patients took the medication exactly as prescribed. The mean treatment duration was about 7 days in all groups.

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 [placebo: 3.3±2.6, EPs 7630 (30 mg): 3.6±2.4, EPs 7630 (60 mg): 4.4±2.4, EPs 7630 (90 mg): 5.0±1.9]. The confirmatory aim of the study was already reached at the interim analysis: All global null hypotheses comparing placebo with all three or to combinations of two active dose levels could be rejected (each $p<0.0001$ except for the comparison placebo vs. 30 mg vs. 60 mg EPs 7630 with $p=0.0011$). The subsequent pairwise comparisons of each active treatment group with placebo using the ANCOVA model revealed statistically significant differences in the decrease in the BSS total score for the EPs 7630 60 mg and 90 mg groups ($p=0.0004$ and $p<0.0001$ respectively, two-sided ANCOVA p-values).

A considerable difference in the BSS total score for the EPs treatment groups was already observed on days 3–5 and increased – in a dose-dependent manner – further until day 7, especially for the dosages of 60 mg and 90 mg.

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 rate of patients in the EPs 7630 (60 mg) and EPs 7630 (90 mg) groups reporting the onset of effect before day 5 was higher than that in the placebo group. A statistically significant advantage regarding the onset of effect in the EPs 7630 (60 mg) and EPs 7630 (90 mg) groups could be demonstrated ($p=0.0060$ and $p<0.0001$, respectively).

The mean decrease in the individual symptoms 'coughing', 'sputum', 'pulmonary rales at auscultation', 'chest pain while coughing' and 'dyspnoea' 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. The active treatment groups showed a significant dose-dependent advantage compared with placebo for the symptoms 'coughing' ($p<0.0001$), 'sputum' ($p=0.0016$) and 'pulmonary rales at auscultation' ($p<0.0001$).

Pairwise comparisons with placebo showed statistically significant advantages of EPs 7630 in the 60 mg and 90 mg group for the symptoms 'coughing' (p=0.0433 and p=0.0002 respectively), 'sputum' (p=0.0499 and p=0.0048 respectively) and 'pulmonary rales at auscultation' (p=0.0014 and p<0.0001 respectively, two-sided t-test, each).

A statistically significant dose-dependent effect of EPs 7630 on the general symptoms 'absence of appetite' (p=0.0234), 'headache' (p=0.0112), 'vomiting' (p=0.0142) from day 0 to day 7 could also be found (Bartholomew test). This was confirmed by pairwise comparisons with placebo, which revealed a significant advantage in the EPs 7630 (90 mg) group regarding the general symptoms 'absence of appetite' (p=0.0128) and 'headache' (p=0.0090).

Between day 0 and day 7, the number of patients able to attend kindergarten, school or work improved markedly in all groups, especially in the EPs 7630 (60 mg) and EPs 7630 (90 mg) groups. At day 0, only 1 patient (1%) was able to attend kindergarten, school or work in the placebo and 60 mg group respectively. At day 7, 33.7% (placebo), 35.0% [EPs 7630 (30 mg)], 44.4% [EPs 7630 (60 mg)] and 53.5% [EPs 7630 (90 mg)] of patients had regained this ability.

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% [23 adverse events in 23 patients; EPs 7630 (30 mg) group], 17.2% [20 adverse events in 17 patients; EPs 7630 (60 mg) group] and 19.2% [19 adverse events in 19 patients; 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% (18 adverse events in 18 patients)]. None of the adverse events was classified as serious.

With 0.008, 0.008 and 0.007 events/days of exposure, the incidence of adverse events in the active treatment groups was in the range of that of placebo (0.006 events/days of exposure), including their putative causal relationship to the study medication.

Assessor's comment:
The study was performed in a non-EU country (Ukraine) and the clinical relevant effect was not predefined. The study was not properly planned, since the different age groups (children between 6-12 years of age and children above 12 years of age) should have been investigated separately. The dosage in this study was different from that of the product (pharmaceutical form tablet) on the market. The dosage of the product depends on the age and children 6-12 years should have taken only 1 tablet (20 mg), twice daily (morning, evening) not three times daily or even more 30 mg three times daily. In comparison with other studies the difference between the effect of EPs 7630 and the placebo for the primary outcome criteria is even less: the decrease of the BSS in the placebo 3.0 (2.6) and in the two higher doses of EPs 7630 4.3 (2.6) for 60 mg group, and 5.0 (1.9) points for the 90 mg group (p=0.0003 and p<0.0001 respectively) which means a difference of 4.3-3.0= 1.3 and 5.0-3.0=2.0, respectively which cannot be considered clinically significant. This article contains many figures and less numerical data, so only the tendency can be seen. It is not known how many percent of patients were free of symptoms considering the single symptoms, or according to IMOS what was the responder's rate. The difference is not meaningful considering the ability to go back to kindergartens or school as well: At day 7, 33.7% (placebo), 35.0% [EPs 7630 (30 mg)], 44.4% [EPs 7630 (60 mg)] and 53.5% [EPs 7630 (90 mg)] of patients had regained this ability. There is not data in the article about withdrawals (only an early dropout is mentioned) and whether there were differences between centres. Conclusion: Although - according to the publications – some effects were seen in secondary parameters, the HMPC concluded that those results cannot be taken as proof on clinical efficacy of the herbal drug preparation from the roots of P. sidoides (1:8–10), dried, extraction solvent: ethanol 11% (w/w). Clinically relevant effects should have been presented for the primary endpoint in which only a small difference has be seen between the effects of the treatment compared to placebo. As this study

has many deficiencies, a conclusion on the efficacy for the solid dosage form in children cannot be drawn from it.

Blochin *et al*. (1999) examined the efficacy and tolerability of Pelargonium extract in comparison to acetylcysteine for children with acute bronchitis in a multicentre, randomized, controlled open trial in Moscow (Russia). Sixty children aged between 5-14 years (1 child less than 6 years in both groups each 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 acetylcysteine granules (2 times 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 lower in the Umckaloabo group than in the acetylcysteine group (33.3% versus 63.3%).

The overall score of bronchitis symptoms varied in both groups between 5 and 15 points and presented a mean value of 7±3 in each group (median: 6) points. The severity of individual symptoms is shown in Figure 27. Cough and sputum were the most common symptoms in both groups. The share of patients with (at least) strong cough was higher in the Umckaloabo group (63.3%) than in the Acetylcysteine group (46.7%).

Statistical analysis. The evaluation was based on an intention-to-treat analysis taking into account all available case reports. 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.

Until the first control examination, the overall score of bronchitis symptoms dropped in both groups from initially 7±3 points by 3±2 points. After 7 days, the overall score of bronchitis 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 bronchitis symptoms was 76.7% in the Pelargonium group and 56.7% in the acetylcysteine group (p=0.17).

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 multi-centre study was performed in a non-EU country in Moscow (Russia); the requirements of ICH E5 (R1) should have been addressed to allow an assessment for the EU.
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 is not in line with the product information. Twenty 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.
Conclusion: The results of this study cannot be considered as an evidence for the efficacy of ethanolic liquid extract in children 6-12 years of age because of inhomogeneity between the two treatment groups. Furthermore the posology was not the same as the one found in the product information.

Kamin *et al*. (2010b) performed a randomized, double-blind, placebo-controlled multicentre trial Placebo-controlled trials to study the efficacy and tolerability of EPs 7630 in children and adolescents with acute bronchitis (Schulz, 2008b; Matthys and Kamin, 2011).

The study was performed in 10 centres in Ukraine from February and April 2006 and included 200 children (EPs 7630: 103; placebo: 97) aged 1 to 18 years: Patients 1 to 6 years: 3 times 10 drops,

patients >6 to 12 years: 3 times 20 drops, patients >12-18 years: 3 times 30 drops per day or matched placebo for 7 consecutive days, preferably administered 30 minutes before meal.

Major inclusion criteria were a total BSS of >5 points and acute bronchitis symptoms having started <48 hours prior to study entry. The individual period of double-blind treatment lasted 7 days including three visits (day 0, day 3 to 5, and day 7).

Major exclusion criteria were: indication for treatment with antibiotics; allergic asthma; tendency to bleed; severe heart, renal or liver diseases and/or immunosuppression, known hypersensitivity against *P. sidoides*; chronic obstructive pulmonary disease and pregnancy.

The primary outcome parameter was the change in the total BSS from baseline to day 7 rated by the investigator. The evaluation of BSS total score comprised the three items „coughing", „pulmonary rales at auscultation" and dyspnoea", which are important features associated with acute bronchitis rated on a scale from 0 (not present) to 4 (very severe) and leading to a maximum total score of 12 points.

Secondary outcome measures were the change in individual symptoms of the BSS; response rates according to three criteria (criterion 1: BSS total score of <3 points on day 7; criterion 2: decrease in BSS total score of at least 4 points from day 0 to day 7 and criterion 3: BSS total score <3 on day 7 combined with a decrease in BSS total score of at least 4 points from day 0 to day 7), change of other general symptoms, e.g. headache, absence of appetite, and vomiting; treatment outcome assessed by both the patient or the legal representatives of the patients (patient's assessment) and the investigator using the Integrative Medicine Outcomes Scale (IMOS); patient's satisfaction with treatment using the Integrative Medicine Patient Satisfaction Scales (IMPSS); onset of treatment effect; ability to attend kindergarten, school or work, and quality of life by means of the FGK questionnaire (i.e. questionnaire for health state of children, which consists of 6 questions). In addition, adverse events (AEs), laboratory safety parameters, and vital parameters were documented.

Baseline parameters showed no baseline difference between the two treatment groups.

At baseline, the mean total BSS was similar in both treatment groups (Figure 28). From baseline to day 7, the mean total BSS improved by 3.4±1.8 points in the EPs 7630 group compared with 1.2±1.8 points in the placebo group ($p<0.0001$, ANCOVA). At Day 7, the response rates according to the different response criteria were considerably higher in EPS 7630 group compared with placebo: (criterion 1: 83.5% vs. 32.0%; criterion 2: 45.6% vs. 13.4%; criterion 3: 45.6 %vs. 13.4%). For all response criteria, a statistically significant difference was determined in favour of EPs 7630 group ($p<0.0001$, two-sided $\chi 2$-test).

The mean decrease in the three individual symptoms of the total score from Day 0 to Day 7 was more pronounced in the EPs 7630 group than in the placebo group with significant advantages for symptoms "coughing" and "pulmonary rales at auscultation".

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 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 $\chi 2$-test). The rates of patients showing complete recovery or major improvement were 77.7% for EPs 7630 and 19.6% for placebo. Patients' IMOS assessments showed a very strong agreement with the assessments.

The onset of treatment effect occurred significantly earlier in the EPs 7630 group as compared to placebo ($p<0.0001$, two-sided Mantel-Haenszel $\chi 2$-test). The rate of patients reporting an onset of treatment effect between Day 1 and Day 2 (18.4% vs. 1%) and between Day 3 and 4 (42.7% vs. 17.5%) was higher in the EPs 7630 group as compared with placebo ($p <0.0001$, two-sided $\chi 2$-test).

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).

The satisfaction of patients with treatment as assessed by the IMPSS on day 7 was also significantly positive in the EPs 7630 group ($p<0.0001$, two-sided Mantel-Haenszel $\chi 2$-test).

Health status and quality of life as assessed by the FGK questionnaire showed significantly better results for the EPs 7630 group compared with placebo. For each FGK statement, namely "everything is too much for me" (1.0±1.2 vs. 0.3±1.3 points, $p<0.0001$), "I am feeling ill" (1.8±0.8 vs. 1.0±1.1 points, $p<0.0001$), "I am scared" (0.8±0.7 vs. 0.3±0.9 points, $p=0.0002$), "I have trouble playing or learning" (1.7±0.9 vs. 0.8±1.1 points, $p<0.0001$), "I sleep bad" (1.6±0.9 vs. 0.9±1.2 points, $p<0.0001$) and "I have problems getting into conversation with others"(1.2±1.0 vs. 0.6±1.0 points, $p=0.0001$), the two-sided t-test showed a significant advantage for the EPs 7630 group compared with placebo. The authors concluded that EPs 7630 was shown to be efficacious and safe in the treatment of acute bronchitis in children and adolescents outside the strict indication for antibiotics and that patients were treated with EPs 7630 perceived a more favourable course of the disease and a good tolerability as compared with placebo.

A total 59 adverse events (AE) were observed in 55 of 200 patients (27.5%). A number of adverse events in the active treatment group (30.1%) was slightly higher than in the placebo group (24.7%). A causal relationship with the study medication could not be excluded for a total of 8 adverse events and was assessed as unlikely. None of the adverse events was classified as serious. The mean values of the clinical laboratory parameters showed no group differences (Kamin *et al*., 2010b).

Assessor's comment:
The study was performed in a non-EU country, in Ukraine. The requirements of ICH E5 (R1) should have been addressed to allow an assessment for the EU.
Similarly to the studies performed in adults here again the predefinition of clinically relevant difference is missing. Although the difference between the effects of the active treatment compared with placebo for the primary outcome is statistically significant, it does not have clinical relevance (3.4±1.8 points in the EPs 7630 group compared with 1.2±1.8, the difference is 3.4-1.2=2.2). In this study the BSS total score (BSS short) comprised only the three items „coughing", „pulmonary rales at auscultation" and dyspnoea", rated on a scale from 0 (not present) to 4 (very severe) and leading to a maximum total score of 12 points. In the aspect of clinical relevance, a 3-point-difference was considered necessary by the Committee in this self-limited disease. (One degree of better improvement in the treatment group. The severity of the disease is mild if the score is 0-3, moderate if it is 6-9, and severe if it is 10-12). At the same time the study was not properly planned, the different age groups should have been investigated separately. A post-analysis was performed but not published. The short BSS is not validated yet, at least not published. There are no data about withdrawals and centre difference in the article.
Conclusion: Although - according to the publications – some effects were seen in secondary parameters the HMPC concluded that these results can not be taken as proof for clinical efficacy of the liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m). Clinically relevant effects should have been presented for the primary endpoint in which only a small difference has been seen between the effects of the treatment compared to placebo. Furthermore, it was not properly planned to investigate the different age groups separately. The short BSS is not validated yet, at least not published.

Two randomized clinical trials have been performed with EPs 76302 for the treatment of acute bronchitis in children and adolescents.

The study by Kamin *et al*. (2012) was conducted between March and May 2006 in 11 Russian centres as a randomized, double-blind, placebo-controlled clinical trial with one adaptive interim analysis. After inclusion in the trial (day 0, visit 1), the baseline examinations were performed. Follow-up examinations were scheduled for day 3–5 (visit 2) and day 7 (visit 3).

A total of 220 patients were included in screening and subsequently randomized to receive placebo or verum containing EPs 7630 (EPs 7630, n=111; placebo, n=109). All randomized patients were included in the safety analysis set for evaluation of tolerability and in the full analysis set for efficacy analysis according to the intention-to-treat principle.

Inclusion criteria: Male or female patients aged 1‑18 years suffering from acute bronchitis with symptoms starting ≤48 hours prior to inclusion in the study and who had a total bronchitis specific symptoms (BSS) score ≥5 points at the time of screening.

Major exclusion criteria were concomitant medication that may impair the study results (e.g. antibiotics, bronchodilators, glucocorticoids, analgesics other than paracetamol, secretolytics, mycolytics, anti-tussiva, or other bronchitis medication); allergic asthma; chronic obstructive pulmonary disease; tendency to bleed; severe heart, renal or liver diseases and/or immunosuppression; known hypersensitivity to *Pelargonium sidoides*; pregnancy.

Patients were randomly given verum containing EPs 7630 or placebo. Placebo was matched with respect to solvent composition, appearance and colour. Dosing of the study drug was 3 times 10 drops corresponding to 0.4 ml of the liquid extract (patients 1–6 years old), 3 times 20 drops corresponding to 0.8 ml of the liquid extract (patients >6–12 years old), or 3 times 30 drops corresponding to 1.2 ml of the liquid extract (patients >12‑18 years old) or placebo per day for 7 consecutive days, preferably 30 min before meal. Paracetamol tablets were allowed if the patient developed fever ≥38.5° C.

The primary efficacy variable was the change in the BSS total score from day 0 to day 7, as rated by the investigator. Evaluation of the BSS total score included the three items 'coughing', 'pulmonary rales at auscultation' and 'dyspnoea'. At each visit, the three symptoms were assessed according to a 5-point verbal rating scale from 0, not present, to 4, very severe. The BSS total score could therefore reach a maximum of 12 points.

Secondary efficacy variables were as follows: response rate defined as BSS total score of <3 points at day 7 (criterion 1), decrease in BSS total score by at least 4 points from day 0 to day 7 (criterion 2), BSS total score <3 at day 7 combined with a decrease in BSS total score by at least 4 points from day 0 to day 7 (criterion 3). Further secondary efficacy variables were: change of the individual symptoms of the BSS total score and change of further general symptoms (lack of appetite, headache, vomiting, diarrhoea), onset of treatment effect, health status and quality of life of patients using the FGK questionnaire (i.e. a questionnaire for health status of children, which consists of six questions addressing health and quality of life; single items are rated on a 5-point verbal scale ranging from 0, not at all, to 4, very distinctive).

Treatment outcome was assessed by both the investigator and the patient using the Integrative Medicine Outcomes Scale (IMOS), a 5-point rating scale consisting of the ratings 'complete recovery', 'major improvement', 'slight to moderate improvement', 'no change' and 'deterioration'. Satisfaction with treatment was assessed using the Integrative Medicine Patient Satisfaction Scale (IMPSS), a 5-point scale consisting of the ratings 'very satisfied', 'satisfied', 'undecided', 'dissatisfied' and 'very dissatisfied'. Additional secondary endpoints were duration of bed rest and ability to attend kindergarten, school or work.

The safety of the investigational medication was documented with respect to frequency, nature and severity of adverse events (AE), vital parameters and laboratory safety parameters.

Statistical analysis. The study was performed with an adaptive interim analysis. Baseline parameters: Evaluation of demographic and anthropometric data indicated no significant differences between the treatment groups.

In relation to the results, from baseline to day 7, the mean BSS total score decreased by 4.4±1.6 points in the EPs 7630 group compared to a decrease of 2.9±1.4 points in the placebo group. A continuous decrease in the mean BSS total score between baseline and day 7 was observed in both treatment groups with a clearly more pronounced decrease in the EPs 7630 group (EPs 7630 vs placebo: day 0, 6.0±1.6 vs 5.8±1.3, p=NS; day 3–5, 3.6±1.4 vs 4.3±1.4, p<0.0001; day 7, 1.6±1.4 vs 2.9 ± 1.4, p<0.0001). Subgroup analysis according to age group (1–6 years old, >6–12 years old, >12–18 years old) indicated comparable statistically significant results (data not shown).

The response rate at day 7 according to all three response criteria was considerably higher in the active treatment group as compared to the placebo group (criterion 1, 81.1% vs 37.6%; criterion 2, 73.9% vs 36.7%; criterion 3, 64.9% vs 24.8%). For all three response criteria, a statistically significant difference was observed for the EPs 7630 group (p<0.0001 each, two-sided $\chi 2$ -test).

With respect to the individual symptoms 'coughing' and 'pulmonary rales at auscultation' the mean decrease in BSS between day 0 and day 7 was more pronounced in the EPs 7630 group as compared with the placebo group (p<0.0001, two-sided t-test, each). The item 'dyspnoea' showed a non-significant advantage for EPs 7630 (data not shown).

With respect to general symptoms, 'lack of appetite' was significantly improved in the EPs 7630 group (p=0.0003) at day 7, according to two-sided t-test. There were no significant differences between both groups concerning the general symptoms 'headache', 'vomiting' and 'diarrhoea'.

The rate of patients reporting an onset of treatment effect between day 1 and 2 (19.8% vs 2.8%) and between day 3 and 4 (51.4% vs 30.3%) was markedly higher in the EPs 7630 group than in the placebo group. Accordingly, the onset of effect occurred significantly earlier in the EPs 7630 group as compared with the placebo group (p<0.0001, two-sided Mantel-Haenszel $\chi 2$-test).

On evaluation of treatment outcome at day 7, patients treated with EPs 7630 had a significantly more favourable IMOS outcome than the placebo group (p<0.0001, two-sided Mantel-Haenszel $\chi 2$-test; the values for the patients' assessment were almost identical to those in the investigators' assessment.

An improvement of health status and quality of life, as assessed on the FGK questionnaire, was seen between day 0 and day 7 for both treatment groups. During the same time period, the number of patients able to attend kindergarten, school or work improved more markedly in the EPs 7630 group. Whereas at baseline, no patient in the EPs 7630 group versus one patient in the placebo group were able to attend kindergarten, school or work, 64 patients (57.7%) in the EPs 7630 group versus 19 patients (17.4%) in the placebo group had regained this ability by day 7.

A total of three AE were observed in two (1.8%) of 111 patients in the EPs 7630 group. These concerned the System Organ Classes 'gastrointestinal disorders', 'infections and infestations' and 'investigations' with one occurrence each. A causal relationship of the adverse events with the investigational medication was excluded in all three cases. None of the adverse events was classified as serious.

Assessor's comment:
The same deficiencies as detected in studies assessed above were also found for Kamin et al. (2010b): the performance of the study in a non-EU country (Russia), missing pre-definition of the clinically

relevant difference, non-validated (at least not published) short BSS (BSS total score included only three items), the difference between the effects of the active treatment compared to placebo for the primary outcome is not considered clinically relevant (4.4±1.6 points-2.9±1.4 points=1.5), the study was not properly planned (the different age groups should have been investigated separately, a post-analysis was performed but not published) and there are no data about withdrawals and centre difference in the article.
Conclusion: Although -according to the publications– some effects were seen in secondary parameters, the HMPC concluded that those results can not be taken as proof for clinical efficacy of the liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m). Clinically relevant effects should have been presented for the primary endpoint in which only a small difference has been seen between the effects of the treatment compared to placebo. Furthermore, the study was not properly planned; the different age groups had to be investigated separately. The short BSS is not validated yet, at least not published.

Haidvogl and Heger (2007) and 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 times 5 drops, 2-6 years: 3 times 10 drops, over 6 years: 3 times 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 bronchitis 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, dyspnoea 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 times 30 drops daily, 6-12 years: 3 times 20 drops per day and <6 years: 3 times 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.

Subgroup analysis for adverse events were conducted for children (aged 3-18 years, n=420) and for infants (aged two years or less n=78). A total of 28 adverse events occurred in 26/2099 patients (1.2%), thereof 14 in children (13/420 patients, 3.1%) and 4 infants (3/78 patients, 3.8%). 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 (1996). The efficacy of EPs 7630 treatment (5-20 times 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).

In a multicentre, prospective, randomised, double-blind, placebo-controlled trial, the efficacy and safety of EPs 7630 (3 times 20 drops daily) was examined and compared to placebo in 143 children aged 6-10 years suffering from acute non-streptococci-induced tonsillopharyngitis in Kiev (Ukraine) (Heger and Bereznoy, 2002; Bereznoy *et al*., 2003). 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).

73 patients received EPs 7630 and 70 patients received matched placebo with regard colour, smell, taste and viscosity. The patients were instructed to take 20 drops 3 times daily (3 ml per day) at 30 minutes before or after the meals starting at day 0 and continuing until day 6.

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 39, Table 13). 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).

Assessor's comment:
Since the Tonsillopharyngitis Severity Score (TSS) is not a validated score, the results of this study are not evaluated.

The more recent study by Gökçe *et al.* (2021) aimed to assess the effectiveness of P. sidoides in pediatric patients diagnosed with uncomplicated upper respiratory tract infections (URTIs). 164 patients (1 to 18 years of age) with URTI were randomized to receive placebo (n=82) or the dry extract (1:8-10), extraction solvent ethanol 11% (w/w) from *P. sidoides* (n=82). Dosing of the study was 3 times 10 drops (= 0.009234 g) for children 1 to 5 years old; 3 times 20 drops (= 0.018468 g)

for children between 5 and 12 years, or 3 times 30 drops (=0.027702 g) for children older than 12 years, at least 30 minutes before or after meals, for 7 days.
The primary outcome criterion was the improvement in the Total Symptom Score from day 0 to day 7. Secondary outcome criteria for effectiveness were the decrease in the severity and duration of the individual symptoms between visit intervals and the benefit of *Pelargonium* preparation in the early stage of URTIs.
After 7 days of treatment, the median of the total symptom score significantly decreased by 0.85 points in the treated group compared to a decrease in 0.62 points in the placebo group (p=0.018). No statistically significant differences were found on baseline, day 3 and day 5.
For the secondary outcome measures, only "cough frequency" showed a statistically significant decrease in the *Pelargonium* group compared to placebo on day 3 (p=0.023), together with a decline in "purulent rhinorrhea" on day 7 (p=0.023).
No adverse events were reported.
Authors considered that the dried root extract of *P. sidoides* may be a supportive treatment for the relief of cough frequency, dry cough and sneezing during uncomplicated URTIs.

Assessor's comment:
Since the Total Symptom Score is not a *validated score, the results of this study are not evaluated.*

The results of clinical studies performed in children are summarized in Table 5.

Table 5: Clinical studies in children, in cough and cold

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%); Quality score (e.g. Jadad score)**	**Comments on clinical relevance of results**
Dose-finding study Kamin *et al*., 2010a	DB, PC, R	EPs 7630 – film-coated tablet 100 patient 3x10 mg 99 patient 3x20 mg 99 patient 3x30 mg placebo duration: 7 days	n=399 age: 6-18 years mean age: 12.7 51.9% male	Acute bronchitis present <48 hours BSS ≥5 points	1st reduction of BSS on day 7 2nd decrease of individual symptoms on day 7 2nd decrease of general symptoms on day 7 2nd adverse events	ITT yes BSS	Not clinically relevant: lack of predefinition of a clinically relevant effect, not adequate design, different dosage than in the marketed product
Comparative study Blochin *et al*., 1999	MC, C, O	*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	n=60 age: 6-12 years mean age: 8.5 vs. 8 33.3% vs. 63.3% male	Acute bronchitis present <48 hours BSS ≥5 points	1st score of bronchitis symptoms at day 7 2nd elimination of individual symptoms on day 7: cough sputum	ITT	Not clinically relevant: non homogeneous distribution among treated groups regarding gender and symptoms severity, different dosage than in the marketed product, no validated score

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%); Quality score (e.g. Jadad score)**	**Comments on clinical relevance of results**
Efficacy and safety assessment Haidvogl and Heger, 2007	MC, O, UC	EPs 7630 >2 years: 3 times 5 drops 2-6 years: 3 times 10 drops 6-12 years: 3 times 20 drops duration: 14 days	n=742 age: 0-12 years <2: 237 2-6: 321 >6: 168 mean age: 4±3 388/742 male	Acute exacerbation of chronic bronchitis (14.3%)	1st reduction of BSS on day 7 on day 14 2nd remission rate of individual symptoms cough sputum dyspnoea rales/rhonchi chest pain 2nd adverse events	BSS	Not oclinically relevant: open uncontrolled study, medication discontinued
Efficacy and safety assessment Matthys *et al*., 2007	MC, P, OO	EPs 7630 >6 years: 3 times 10 drops 6-12 years: 3 times 20 drops >12 years: 3 times 30 drops duration: 14 days	n=498 >6-12: 127 <=6: 241 years: 0-18	Acute bronchitis productive cough for less than 6 days	1st decrease of BSS 1st follow-up 2nd follow-up 3rd follow-up 2nd adverse events	BSS	Not oclinically relevant: open uncontrolled study
Efficacy and safety assessment Kamin *et al.,* 2010b	DB, PC, R	EPs 7630: 103 patients 1-6 years: 3 times 10 drops 6-12 years: 3 times 20 drops 12-18 years: 3 times 30 drops	n= 200 age: 1-18 years mean age: 9	Acute bronchitis present < 48 hours BSS ≥ 5 points	1st reduction of BSS on day 7 2nd adverse events	ITT yes BSS	Not clinically relevant: Lack of predefinition of clinically relevant effect, not fulfilling ICH E5 requirements, Short BSS, not

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%); Quality score (e.g. Jadad score)	Comments on clinical relevance of results
		Placebo: 97 patients duration: 7 days					validated
Efficacy and safety assessment Kamin *et al*., 2012	MC, R, DB, PC	EPs 7630 : 111 patients 1-6 years: 3 times 10 drops 6-12 years: 3 times 20 drops 12-18 years: 3 times 30 drops Placebo: 109 patients duration: 7 days	n=220 age: 1-18 years mean age: 9	Acute bronchitis present <48 hours BSS ≥5 points	1st reduction of BSS on day 7 2nd adverse events	CI 95% BBS IMOS	Not clinically relevant: Lack of predefinition of clinically relevant effect, not fulfilling ICH E5 requirements, Short BSS, not validated
Efficacy and safety assessment Heger and Bereznoy, 2002; Bereznoy *et al.*, 2003	MC, R, DB, PC	73 patients EPs 7630 20 drops, 3 times daily 70 patients placebo duration: 6 days	n=143 age: 6-10 years mean age: 7.5 49% male	non-Streptococci-induced Tonsillopharyngitis present <48 h	1st change of TSS on day 4 2nd remission rate of tonsillitis specific symptoms dysphagia sore throat fever 2nd adverse events	TSS	Not clinically relevant: TSS not validated
Efficacy	SB, R, PC	82 patients Dry extract (1:8-	n=164 age: 1-18 years	URTIs	1st improvement in the Total Symptom	ITT yes Total symptom	Not clinically relevant: Total

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%); Quality score (e.g. Jadad score)	Comments on clinical relevance of results
Gökçe *et al*., 2021		10), extraction solvent ethanol 11%(w/w) from *P. sidoides* 1 to 5 years: 3 times 10 drops (= 0.009234g) 5-12 years: 3 times 20 drops (= 0.018468g) >12 years: 3 times 30 drops (=0.027702g) At least 30 minutes before or after meals, for 7 days	mean age: 4.85 46% male		Score from day 0 to day 7 2nd decrease in the severity and duration of the indicidual symptoms between visit intervals and benefit of in the early stage of URTIs	score	symptom score not validated

4.4. Overall conclusions on clinical pharmacology and efficacy

Studies in adults

The four clinical studies (including one dose finding study) used the same methods to measure the efficacy and the safety of EPs 7630 preparation compared to placebo. The same inclusion and exclusion criteria were applied. 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. The same or similar secondary outcome criteria were measured as well.

In the first version of assessment report on the Pelargonii radix the clinical studies performed with EPs 7630 product were not evaluated due to the lack of validation of Bronchitis Severity Scale (BSS) used as primary evaluation criterion and so the monograph contained only traditional use indication. After the first publication of the monograph (20 November 2012) the marketing authorisation holder of EPs 7630 product submitted to the Committee a document consisting of a retrospective validation of Bronchitis Severity Scale (BSS) (Lehrl, 2012) which was later published as well (Matthys and Kamin, 2013; Kardos *et al*., 2014; Lehrl *et al*., 2014). Following the assessment of newly submitted data, the HMPC considered the BSS to be an acceptable, valid measuring instrument (7 June 2013 EMA/HMPC/301544/2013). However, acceptance of Bronchitis Severity Scale/Score (BSS) as validated method for clinical evaluation of medicines used in patients in the therapeutic area 'cough and cold' has not meant automatic acceptance of all the studies which used this method.

So this updated assessment report evaluated the four clinical studies (including one dose-finding trial) performed in adults patients with acute bronchitis in order to decide whether products containing *Pelargonium sidoides* extract can fulfil the requirements of 'well-established medicinal use' as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety.

Only data published in literature were evaluated since in the case of an „active substance(s) of which has/have a 'well-established medicinal use' a „detailed scientific bibliography shall address non-clinical and clinical characteristics" (see 2001/83/EC Directive, Part II 1. Well-established use).

The results of the tree placebo controlled clinical studies (Golovatiuk and Chuchalin 2002) later published by Chuchalin *et al*. 2005; Matthys *et al*., 2003; Matthys and Heger, 2007a (Table 5)) which were conducted with the liquid preparation [DER 1:8-10, extraction solvent ethanol 11% (m/m), 1.2 ml three times daily] cannot be accepted as evidence of efficacy.

Although in all studies it was concluded that the differences between the decrease in the BSS when comparing the EPs 7630 solution to placebo (7.2-4.9=2.3 for Golovatiuk and Chuchalin (2002) 5.9-3.2=2.7 for Matthys *et al*. (2003) and 7.6-5.3=2.3 for Matthys and Heger (2007a)) were statistically significant ($p<0.0001$, each), none of authors mentioned whether and which difference was predefined as clinically relevant effect considering the primary outcome criterion.

A general agreement on this requirement for BSS cannot be found in the literature and HMPC also did not discuss this issue when evaluated the validation of BSS as a method in 2013.

During the public consultation on the previous updated Assessment report (published on 26/10/2015) the Company suggested different methods to measure the efficacy:

- comparison the BSS (day 0) total score at baseline with the BSS total score at study end under consideration of 20% difference.
- a difference of 20% of the observed scale range

- Cohen's d methods (the difference in means (e.g. between Verum and Placebo) divided by the pooled standard deviation as a measure of variability.)

However, these methods were not accepted since they do not consider the seriousness of the disease: the milder the disease is the smaller difference is considered clinically relevant.

According to the Company even 'the difference of 1 point of the BSS may mean, e.g. the reduction of cough from "mild" to "absent". For a patient this can very well mean a clinically relevant improvement of his/her condition.'

This was not endorsed as well since if the cough were the single primary endpoint then one-point difference could be a clinically relevant improvement, if justified by the authors of the study. However, there are five items: cough, sputum, rales/rhonchi, chest pain during coughing and dyspnoea. Each item can receive 0-4 points according to the severity of symptoms.

During the assessment of clinical studies with EPs 7630, the HMPC decided that in this self-limiting disease one grade of better improvement in the treatment group compared to the placebo group is considered clinically relevant. The severity of the disease is mild if the score is 0-5, moderate if it is 6-10, and severe if it is 11-15 and so on. There is a clinically relevant improvement if the severity of the disease decreases one grade for example from moderate to mild. It means 5 point of decrease. If sputum is disregarded because it existed only for some patients so 4 points of decrease can be considered as clinically relevant improvement. However, this is only a general recommendation. The definition of the clinical relevance should be determined for each therapeutic field, for every clinical study individually already before the start of the study, under consideration of the circumstances of the specific patient population.

None of the tree placebo controlled clinical studies could meet this requirement: the difference was 2.3 for Chuchalin *et al*. (2005), 2.7 for Matthys *et al*. (2003) and 2.3 for Matthys and Heger (2007a). Moreover, in the Matthys *et al*. 2003, study there was a high number of drop-outs (38.9%) from the placebo group, which could distort the results. According to another article (Lehrl *et al*., 2014) there was difference between the investigation sites: "One study was subdivided into two sections (Matthys *et al.,* 2003), because one part was performed in Germany with German doctors and patients and the other in Ukraine with Ukrainian doctors and patients. Possibly the different backgrounds of history and native language could exert different influences on the results".

This brings up another problem that the study was performed in non-EU country, in the territory of Russian Federation. Although it is a requirement of the international guidance (ICH Topic E 5) but the publication did not discussed whether the results can be extrapolated for EU.

Since the dose-finding study performed with the solid dosage form (Matthys *et al*., 2010b) was only an exploratory study to determine the effective dose and it has the same deficiencies as mentioned above for the solution (it was performed in Ukraine, the clinically relevant difference between the effect of the extract and the placebo was not predefined, and the found difference cannot be considered large enough, mean BSS score decreased by 2.7±2.3 for placebo, 4.3±1.9 for 30 mg group, 6.1±2.1 for 60 mg group and 6.3±2.0 points for 90 mg group, respectively) so a decision about the efficacy of this pharmaceutical form cannot be made. In addition, the article provided very few numerical data; most of the results are presented only by figures, which show only the tendencies. For example, it would be good to know how many percent of patients was free of symptoms by the end of treatment in the different treatment groups in this self-limiting disease. Whether there was a difference between the 16 centres considering the efficacy.

Studies in children and adolescents

Considering the studies performed in children and adolescents one comparative study and four placebo-controlled studies were published in the literature.

The comparative study with acetylcysteine has methodical failures. 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. Twenty 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. Moreover, the study was performed in a non-EU country, in Moscow (Russia).

The two placebo controlled studies with the EPs 7630 solution (Kamin *et al.*, 2010b and Kamin *et al*., 2012) were performed in non-EU countries in Ukraine and in Russia. The definition of response criteria was adopted taking into account 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, this so-called "BBSshort" was considered for confirmatory analysis in the total population comprising "coughing", "pulmonary rales at auscultation" and "dyspnoea" only. This led to a maximal score of 12 points instead of 20 possible points.

The results of the two placebo controlled studies showed a statistically difference between the EPs 7630 and placebo group but similarly to the studies performed in adults in these articles there was not predefined how big a difference would be considered clinically relevant. HMPC did not find the differences to be clinically relevant.

As for BSS short there is also not a general agreement how many points of difference between the treatment and the placebo shows a clinically relevant effect, a 3 point of difference was considered a big enough in this self-limited disease by the Committee (one degree of better improvement in the treatment group. The severity of the disease is mild if the score is 0-3, moderate if it is 6-9, and severe if it is 10-12).

In addition, all these studies were not properly planned; the different age groups should have been investigated separately. Post-analyses were performed but not published. The short BSS is not validated yet, at least not published. There are no data about withdrawals and centre difference in the articles as well.

Additional to all the other points (non-EU-study, missing pre-definition of clinical relevant differences in the primary endpoint) the dose finding study in children with the solid dosage form was only an explanatory study; also therefore, a decision about the efficacy of this pharmaceutical form cannot be made.

The studies by Heger and Bereznoy (2002) (also published by Bereznoy *et al.*, 2003) and Gökçe *et al*., 2021 were two placebo-controlled studies in which a not validated score was applied (Tonsillopharyngitis Severity Score and Total Symptoms Score, respectively). Thus, although there was a stratification in the different age groups related to dosification and investigation, they can not be evaluated in relation to *Pelargonium* efficacy.

Overall conclusion on placebo controlled studies performed with EPs 7630 extracts (both children and adults)

The published studies have similar deficiencies. They were performed in non-EU countries (Ukraine and Russia) and although it is a requirement according to the guidance document [ICH Topic E 5 (R1), September 1998 CPMP/ICH/289/95], in the articles it was not discuss whether the results can be extrapolated to EU-countries or not.

Although ICH-Guidelines E8 and E9 state that the primary endpoint(s) should reflect clinically relevant effects, which should be defined prospectively, the articles did not mention whether and which

difference between the treatments with Pelargonium extract and placebo in the primary outcome criterion (decrease in the Bronchitis Specific Symptoms Score) was considered clinically relevant.

In the absence of such a definition made by the investigator, the HMPC considered that a strong effect is needed to claim clinical relevance because acute bronchitis is a self-limiting disease.

In this self-limiting disease one grade of better improvement in the treatment group compared with the placebo group is considered clinically relevant. At least 4 points of difference between the active treatment group and the placebo group in the decrease of total BSS from the baseline to the end of the treatment are considered as strong clinically relevant difference in the case of adults and 3 points in the case of children (BSSshort). However, none of these studies could present these differences.

A better result might have been reached if more serious cases of the disease had been included into the clinical studies. BSS on Day 0 was only 9.0±2.2 [8] in the EPs 7630 group and 9.1±2.2 [8] in the placebo group in the Chucahalin *et al.,* 2005 study and 8.9±1.6[9] in EPs 7630 and 8.4±1.8[8] in placebo in the Matthys and Heger (2007a) study, which means only a moderate form of acute bronchitis.

For example, a result which can be accepted is a 5.8 - difference in the BSS between the effect of the treatment group compared with the placebo group - as seen in a study performed by Gruenwald *et al*. (2005) with a fixed combination of thyme ad primrose root in patients with acute bronchitis. The Day 0 BSS was higher: 12.0±4.4 points in the verum group 11.7±4.3 points in the placebo group.

Although the results of open studies are also promising, the lack of a true control group, blinding and randomisation limits the usefulness of these trials.

Taking into account the above mentioned deficiencies, the HMPC concluded that the clinical studies published in the literature cannot prove adequately the efficacy of EPs 7630 in acute bronchitis in adults, adolescents or children.

The evaluation of the effects of the drug in adult patients with acute sinusitis was based on two trials (Schapowal and Heger, 2007; Bachert *et al*., 2009). These studies showed significant treatment effects for the alleviation of symptoms. Considering the small sample size and the lack of control in case of one study, 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).

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).

Table 6.1: Clinical safety data from clinical trials in adults

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration; Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Adverse reactions**	**Comments on clinical relevance of results**
Dose-finding trial Matthys *et al*., 2010b	R, PC, DB	EPs 7630 film-coated tablet 10, 20, 30 mg *versus* placebo, 3 times daily Duration: 7 days	n=405 adults (>18 years old)	Adults suffering from acute bronchitis ≤48 hours prior to inclusion the study and total score of bronchitis–specific symptoms ≥5 points at screening	92 mild or moderate adverse events observed in 18.5% of patients: GI disorders: 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). None of the adverse events was classified as serious. GI disturbances increased dose-dependently	GI disorders were present in both placebo and treated groups, but showed a dose-dependent increase in the treated groups. It is mentioned in the monograph.
Efficacy and safety assessment Golovatiouk and Chuchalin, 2002	DB,PC,R	Test product: EPs 7630 Oral liquid 30 drops, 3 times daily Duration: 7 days	n= 124 between 18-71years male: 23.4 vs. 36.7%	Acute bronchitis present (≤48 hours) BSS ≥5 points	25 out of 124 patients (20.2%) experienced at least one AE: 15 out of 64 (23.4%) in the treated group and 10 out of 60 (16.7%) in the placebo group. GI disorders (mild to moderate)	GI disorders were present in both placebo and treated group. It is mentioned in the monograph.
Efficacy and	DB,PC,R	Test product: EPs	n= 468	Acute bronchitis	26 AE for treated	GI disorders.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration; Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse reactions	Comments on clinical relevance of results
safety assessment Matthys *et al*., 2003[#]		7630 Oral liquid 30 drops, 3 times daily Duration: 7 days	mean age: 41.1 vs.39.9 male: 40.3 vs. 46.9%	present (≤48 hours) BSS ≥5 points	patients and 11 for the placebo group GI disorders, nervous system disorders, respiratory/thoracic and mediastinal disorders, and ear and labyrinth disorders	Both GI and hypersensitive reactions are mentioned in the MO
Efficacy and safety assessment Matthys and Heger, 2007a*, Matthys and Funk, 2008	DB,PC,R, MC	Test product: EPs 7630 Oral liquid 30 drops, 3 times daily Duration: 7 days	n= 217 mean age: 37.4 male: 24.4%	Acute bronchitis present (≤48 hours) BSS ≥5 points	No serious adverse events recorded 21.7% (47/217) patients experienced at least one AE: 21.3% (23/108) patients in the treated group and 22.0% (24/109) in the placebo group. No relevant difference in the distribution of the adverse events over the different treatment groups	Mainly GI disorders. It is mentioned in the monograph.
Efficacy and safety assessment Matthys *et al*., 2007	MC, P, OO	EPs 7630 Oral liquid 30 drops, 3 times daily duration: 14 days	n= 2099 mean age: 34.5 41% male	Productive cough for less than 6 days	28 (non serious) AEs: 11 out of 28 were GI disorders	GI disorders. It is mentioned in the monograph.
Efficacy assessment Matthys and	MC, P, OO	EPs 7630 Oral liquid 30 drops, 3 times	n= 205 mean age: 42 33.2% male	acute bronchitis (87.8%) or acute exacerbation of chronic bronchitis	18 (non serious) AEs: 11 out of 18 were GI disorders	GI disorders. It is mentioned in the monograph.

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration; Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse reactions	Comments on clinical relevance of results
Heger, 2007b[#]		daily duration: 7days		present (≤7 days)		
Efficacy assessment Schapowal and Heger, 2007	MC, O	EPs 7630 adults: 30 drops every hours up to 12 times on day 1 and 2; 3 times 30 drops daily from day 3 Children (<12 years): 20 drops every hours up to 12 times on day 1 and 2; 3 times 20 drops daily from day 3 duration: Acute sinusitis: 28 days Exacerbation: 28 days+ 8 weeks prophylaxis–(2 times 30 drops daily for adults and 2 times 20 drops daily for children)	n=361 1-94 years mean age: 38±19	acute sinusitis or acute exacerbation of chronic sinusitis	56 out of 361 (15.5%) AEs, mostly GI complaints	GI disorders. It is mentioned in the monograph.
Efficacy and safety assessment	DB,PC,R, MC	EPs 7630 60 drops, 3 times daily duration:	n=103 mean age: 34.4 vs. 35.6 37% vs. 33%	Acute rhinosinusitis present at least 7 days SSS ≥12 points	8 out of 103 patients with at least 1 (non-serious) AE: 6/51 in the treated group	GI disorders. Both GI and hypersensitive reactions are mentioned in the MO

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration; Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Adverse reactions	Comments on clinical relevance of results
Bachert *et al*., 2009*		maximum 22 days	male		- GI complaints (3) - Allergic skin reaction (1) and 2/52 in the placebo group	
Efficacy and tolerability assessment Lizogub *et al*., 2007*	DB,PC,R, MC	EPs 7630 30 drops, 3 times daily duration: maximum 10 days	n=103 mean age: 34.5 vs. 37.4 30.7% vs. 31.3% male	Common cold present 24-48 hours maximum symptoms score 40	3 out of 103 patients with (non-serious) AEs: 2/52 (3.8%9 in the treated group and 1/51 (2%) in the placebo group	AE unrelated to the study drug

Table 6.2: Clinical safety data from clinical trials in children and adolescents

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration; Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Adverse reactions**	**Comments on clinical relevance of results**
Dose-finding study Kamin *et al.,* 2010a	DB, PC, R	EPs 7630 – film-coated tablet 100 patient 3x10 mg 99 patient 3x20 mg 99 patient 3x30 mg placebo duration: 7 days	n=399 age: 6-18 years mean age: 12.7 51.9% male	Acute bronchitis present <48 hours BSS ≥5 points	80 (non-serious) adverse events in 77 of 400 patients (19.3%): - GI disorders (11%). Frequency of adverse events in the active treatment groups similar to that in the placebo group [17.8% (18 adverse events in 18 patients)].	GI disorders. It is mentioned in the monograph.

Comparative study Blochin *et al*., 1999	MC, C, O	*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	n=60 age: 6-12 years mean age: 8.5 vs. 8 33.3% vs. 63.3% male	Acute bronchitis present <48 hours BSS ≥5 points	None	
Efficacy and safety assessment Haidvogl and Heger, 2007	MC, O, UC	EPs 7630 >2 years: 3 times 5 drops 2-6 years: 3 times 10 drops 6-12 years: 3 times 20 drops duration: 14 days	n=742 age: 0-12 years <2: 237 2-6: 321 >6: 168 mean age: 4±3 388/742 male	Acute exacerbation of chronic bronchitis (14.3%)	13 AEs: exanthema, psychomotor unrest with crying fits, dyspnoea, diarrhoea	Both GI and hypersensitive reactions are mentioned in the MO
Efficacy and safety assessment Matthys *et al*., 2007	MC, P, OO	EPs 7630 >6 years: 3 times 10 drops 6-12 years: 3 times 20 drops >12 years: 3 times 30 drops duration: 14 days	n=498 >6-12: 127 <=6: 241 years: 0-18	Acute bronchitis productive cough for less than 6 days	28 adverse events in 26 patients - infections and infestations (not related to study medication) - hypersensitive reaction	Hypersensitive reactions are mentioned in the MO

Efficacy and safety assessment Kamin *et al.,* 2010b	DB, PC, R	EPs 7630: 103 patients 1-6 years: 3 times 10 drops 6-12 years: 3 times 20 drops 12-18 years: 3 times 30 drops Placebo: 97 patients duration: 7 days	n= 200 age: 1-18 years mean age: 9	Acute bronchitis present < 48 hours BSS ≥ 5 points	59 (non-serious) adverse events observed in 55 of 200 patients (27.5%). Adverse events in the treatment group (30.1%) slightly higher than in the placebo group (24.7%).	GI disorders were present in both placebo and treated group. It is mentioned in the monograph.
Efficacy and safety assessment Kamin *et al*., 2012	MC, R, DB, PC	EPs 7630 : 111 patients 1-6 years: 3 times 10 drops 6-12 years: 3 times 20 drops 12-18 years: 3 times 30 drops Placebo: 109 patients duration: 7 days	n=220 age: 1-18 years mean age: 9	Acute bronchitis present <48 hours BSS ≥5 points	3 (non-serious) adverse events observed in 2 (1.8%) of 111 patients in the treated group: - GI disorders - infections and infestations - investigations Causal relationship excluded in all three cases.	GI disorders. It is mentioned in the monograph.
Efficacy and safety assessment Heger and Bereznoy, 2002; Bereznoy *et al*., 2003	MC, R, DB, PC	73 patients EPs 7630 20 drops, 3 times daily 70 patients placebo duration: 6 days	n=143 age: 6-10 years mean age: 7.5 49% male	non-Streptococci-induced Tonsillopharyngitis present <48 h	Adverse events in 1/73 in the treated group and 14/70 in the placebo group All events represented typical symptoms of the acute infection. None of the cases was correlated with the test medication.	Not clinically relevant as symptoms were related to the disease itself.

Kamin *et al*., 2023	Open label, R	403 patients EPs 7630 syrup 188 patients Eps 7630 solution Syrup: 2.5ml, 3 times daily Solution: 10 drops, 3 times daily duration: 7 days	n=591 age: 1-5 years mean age: 3 53% male	Acute bronchitis	Infections (syrup: 2.7%; solution: 3.2%) Gastrointestinal disorders (syrup; 2.7%, solution: 3.2%) At treatment end, an elevation of at least one hepatic enzyme (ALT, AST, γGT) activity in 4.1% (95% CI: 2.6%, 6.0%) of study participants compared to 5.7% (95%CI: 3.9%, 7.9%) at baseline	Both preparations shown equal safety and well tolerance

5.2. Patient exposure

The clinical trials referred in this assessment report were conducted on over 3,500 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, serious adverse events and deaths

There is a large number of studies and the section 4.2 and Table 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, bronchitis 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 study by Kamin *et al* (2023) was an open-label, randomized study in children aged 1-5 years with acute bronchitis aimed to compare the safety of two different preparations from *Pelargonium* root (EPs7630): syrup or (ethanolic) solution. 591 children were randomized and treated with syrup (n=403) or solution (n=188) for 7 days. Patients received 2.5 ml of syrup, 3 times daily or 10 drops of solution, 3 times daily.

Safety was assessed by frequency, severity, and nature of adverse events (AE), vital signs (heart rate, respiration rate, body temperature) and laboratory values (ALT, AST, γGT, c-reactive protein-CRP). After 7 days of treatment, the number of AE was similarly low and revealed no safety concerns; the most frequently observed adverse events were infections (syrup: 7.2%, solution 7.4%) or gastrointestinal disorders (syrup: 2.7%, solution: 3.2%). At treatment end, an elevation of at least one hepatic enzyme (ALT, AST, γGT) activity was observed in 4.1% (95% CI: 2.6%, 6.0%) of study participants compared to 5.7% (95%CI: 3.9%, 7.9%) at baseline; there was no upward shift of mean activity values after 7 days of treatment.

In summary, suspected cases of adverse drug reactions were observed in less than 2% of the study participants. These events were gastrointestinal disturbances and elevated hepatic enzymes and, in all cases, causality was assessed as "unlikely", except for one case of diarrhoea ("possible"). Nevertheless, the percentage of patients with elevated hepatic enzyme activities was higher at baseline than after the treatment period, and all elevations were below the limit of 5-fold of upper limit of normal and therefore below the threshold indicative of liver injury (Teschke and Danan, 2021). All cases of increased enzyme activities may be related to the underlying or concomitant viral infections.

Authors concluded that both preparations, syrup and oral solution, were equally safe and well tolerated in children aged 1-5 years suffering from acute bronchitis, although the open label design and the lack of a placebo group are the main limitations to assess the efficacy of this investigation (Kamin *et al*., 2023).

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. dyspnoea, 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-prick 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 co-medication 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*., 2008).

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.* (2012a) re-evaluated the data of these patients 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 co-medicated 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 co-medication 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 co-medication, 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 pre-existing 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.

Germany also requested information from other countries through the system "Non urgent information" and based on all the available information the Summary of Product Characteristics of the products marketed in Germany had 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 the medicinal product. In case of signs of hepatotoxicity occur, the application 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 the medicinal product. 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; *Pelargonium reniforme* Curt., radix was put on the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs) which are required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC except for products referred in Article 14 of Directive 2001/83/EC. This assessment report covers the PSURs submitted for the active substance for a reporting period of 10 years, spanning from 2 June 2013 to 1 June 2018 and 2 June 2018 to 1 June 2023.. During the period under review, a total of 1097 Individual Case Safety Reports (ICSRs) that occurred during the use of medicinal products containing EPs 7630 were reported spontaneously. Hepatotoxicity has been closely monitored by MAHs in the review period. Hepatobiliary disorders such drug–induced liver injury, acute hepatitis, hepatotoxicity continue to be reported, although in a very low number (9 serious cases) compared to the patient exposure (several millions of patient-days). In conclusion, the risk-benefit ratio remains unchanged and positive when used according to the approved terms of the marketing authorisations.

No new information on suspected side effects, exposure during pregnancy and lactation, long-term treatment, off-label use, contraindications, interactions or tolerance of EPs 7630 containing medicinal products has been detected which would affect the risk-benefit balance. Other adverse reactions reported with higher disproportionality rate in Eudravigilance (EV) such as gastrointestinal disorders, hypersensitivity reactions, skin and subcutaneous tissue disorders, respiratory disorder are already addressed in the SmPC of the original product.

From available published case reports and clinical studies, the following information and table is added to the monograph section 4.8 'Undesirable effects': (all symptoms are stated according to MedDRA-terminology and classified according to the most relevant SOC related to the target organ).

System organ classes (SOC)	**MedDRA-terms**	
Immune system disorders	Hypersensitivity, (anaphylactic reaction)	Frequency not known
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria, angioedema	Frequency not known

Respiratory, thoracic and mediastinal disorders	Nasal bleeding	Frequency not known
Gastrointestinal disorders	Diarrhea, epigastric pain, nausea, vomiting, gingival bleeding	Frequency not known
Hepatobiliary disorders	Liver disorders, hepatitis	Frequency not known

Assessor's comment:
The safety profile of Pelargonium sidoides DC; *Pelargonium reniforme* Curt., radix *as an active substance remains unchanged and data obtained during the reporting interval remains consistent with previous knowledge. All safety information that emerged during the reporting period is adequately and correctly addressed in the product information of the original products and no further actions are warranted this time.*
The benefit-risk balance of P. sidoides DC and/or *P. reniforme* Curt*. radix containing medicinal products remains unchanged when used according to the approved terms of the marketing authorisations.*

5.4. Laboratory findings

The study by Kamin *et al* (2023) aimed to assess the safety of EPs7630 (in the form of syrup or solution) in children aged 1-5 years with acute bronchitis. Patients received 2.5 ml of syrup, 3 times daily or 10 drops of solution, 3 times daily for 7 days. Safety was assessed by frequency, severity, and nature of adverse events (AE), vital signs (heart rate, respiration rate, body temperature) and laboratory values (ALT, AST, γGT, c-reactive protein-CRP). At treatment end, an elevation of at least one hepatic enzyme (ALT, AST, γGT) activity was observed in 4.1% (95% CI: 2.6%, 6.0%) of study participants compared to 5.7% (95%CI: 3.9%, 7.9%) at baseline; there was no upward shift of mean activity values after 7 days of treatment.

The percentage of patients with elevated hepatic enzyme activities was higher at baseline than after the treatment period, and all elevations were below the limit of 5-fold of upper limit of normal and therefore below the threshold indicative of liver injury (Teschke and Danan, 2021). All cases of increased enzyme activities may be related to the underlying or concomitant viral infections.

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 (2007a) 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 of 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 reported in 6 cases and found decreased, but in none of the overall 13 patients ALT normalisation has been reported (Teschke *et al*., 2012b).

Among the 15 study patients analysed by 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 pre-existing 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

No information available.

5.5.1. Use in children and adolescents

For every preparation, the oral use in children under 3 years of age is not recommended because of concerns requiring medical advice related to the disease.

5.5.2. Dry extracts: The herbal preparations b) and c) should be given to children under 6 years only in liquid dosage formsContraindications

Hypersensitivity to the active substance(s).

5.5.3. Special Warnings and precautions for use

Hepatotoxicity and hepatitis cases were reported in association with the administration of the medicinal product (see chapter 5.3). In case signs of hepatotoxicity occur, the administration of the medicinal product should be stopped immediately and a medical doctor should be consulted.

5.5.4. Drug interactions and other forms of interaction

None reported.

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 times 1 tablets of penicillin alone (n=13) or in co-medication with 3 times 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).

On the basis of available non-clinical and limited clinical data, it was assumed in literature 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).

5.5.5. Fertility, pregnancy and lactation

No fertility data available.

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

5.5.6. Overdose

No information is available on overdose

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

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

The ethanol content of preparations from *Pelargonium* roots may influence the ability to drive.

5.5.8. Safety in other special situations

To date, neither safety studies in individuals with hepatic nor with renal disease, have been performed.

5.6. Overall conclusions on clinical safety

On the basis of available safety data from clinical and post-marketing trials with pelargonium preparations, the liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m), and its corresponding (in the sense of R8 of the "Regulatory questions and answers on herbal medicinal products" (EMA/HMPC/345132/2010 Rev.5)) dry extracts from Pelargonii radix (dry extract (DER 4-25:1), extraction solvent ethanol 11% (m/m) and dry extract (DER 4-7:1), extraction solvent: ethanol 14% (V/V)) prove not to be harmful in the specified conditions of use for the symptomatic treatment of common cold.

For Pelargonium preparations, pharmacovigilance and scientific literature data are available which support the safe use in children from 3 years of age (see section 5.5.1).

6. Overall conclusions (benefit-risk assessment)

Based on the available clinical data, the efficacy of the solution of Pelargonii radix in the symptomatic treatment of moderate acute upper respiratory infection has not been proven adequately in adults, in adolescents and in children.

The specific pelargonium extract EPs 7630 has been on the market for more than 10 years for the therapeutic indication "acute bronchitis" and some other requirements of the well-established medicinal use (Article 10a 2001/83/EC Directive) are also met.

- Pelargonium products have widespread use, since they are authorised/registered in 15 countries in the European Union.
- There exists scientific interest in the use of the substance since reviews and meta-analysis discuss its effect (Agbabiaka *et al*., 2008; Cochrane reviews by Timmer *et al*., 2008 and 2013), but the studies were performed by all the same investigators (the manufacturer) and in the same region (Ukraine and Russia).

However, the HMPC was the opinion that the placebo-controlled studies with Pelargonii radix were not adequate to prove the efficacy of the liquid preparation [DER 1:8-10, extraction solvent: ethanol 11% (m/m)]. The studies were performed mainly in non-EU countries and the pre-definition of the clinically relevant difference between two treatments in the primary outcome criterion (decrease in the BSS) was missing.

In the absence of such a definition by the investigator, the HMPC considered that a strong effect is needed to claim the clinical relevance since acute bronchitis is a self-limiting disease. In this self-limiting disease one grade of better improvement in the treatment group compared with the placebo group are considered clinically relevant. At least 4 points of difference between the active treatment group and the placebo group in the decrease of total BSS from the base line to the end of the treatment are considered as strong clinically relevant difference in the case of adults and 3 points in the case of children (BSSshort). However, none of these studies showed these differences.

Moreover, the published clinical studies performed in children and adolescents have other methodical shortcomings. In the comparative study (Blochin *et al*., 1999), 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. The two placebo-controlled studies (Kamin *et al*., 2010b and Kamin *et al.*, 2012) were not properly planned, the different age groups should have been investigated separately. Although the short BSS for paediatrics has been validated and the validation has been published (Lehrl *et al*., 2018), the study conducted by Gökçe *et al.* (2021) in paediatric patients (1-18 years) diagnosed with uncomplicated upper respiratory tract infections were performed in a non-EU country and used a different score (Total Symptom Score) to assess the efficacy of the treatment; as it is not a validated score, the results of this study can not be taken into consideration.

One dose finding study was conducted with the solid dosage form, the different age groups were not evaluated separately, and the posology was not adapted to the age. The results in the primary and secondary parameters were not adequate.

According to the market overview, the liquid extract of Pelargonii radix has been on the market for more than 30 years with the indication acute bronchitis. Therefore, this preparation meets the requirement of traditional use in the meaning of Directive 2004/24/EC. However, since this indication needs medical diagnosis and supervision, the following indication was accepted for the traditional use: *Traditional herbal medicinal product for the symptomatic treatment of common cold.*

This is in line with registrations of THMPs with the same composition in several Member States. From the aspect of traditional use - in accordance with the Directive 2004/24/EC - two dry extracts are considered to be corresponding to the above mentioned liquid extract and can be included in the traditional use side of the monograph.

Thus, traditional use has shown *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix preparations:

- Liquid extract (DER 1:8-10), extraction solvent: ethanol 11% (m/m)
- Dry extract, DER (4-25:1), extraction solvent: ethanol 11% (m/m)

- Dry extract DER (4-7:1), extraction solvent: ethanol 14% (V/V)

can be recognized as safe when used in recommended dosages under the conditions specified in the monograph, in adults and children from 3 years of age, for the following therapeutic indication:

Traditional herbal medicinal product for the symptomatic treatment of common cold.

In the studies on the treatment of respiratory infections with an extract of *P. sidoides,* the adverse events were assessed as being non-serious, minor, or transitory. In a review article about the treatment of acute bronchitis with Pelargonium extract, the most frequent adverse events were mild 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 preparations (Conrad and Schulz, 2007).

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. Other countries were also requested to give information by the EMA "Non urgent information" system. Based on all the available information BfArM concluded that there is at least a possible association between *Pelargonium* application and hepatotoxicity. The risk of possible hepatotoxicity is reflected in sections 4.4 and 4.8 of the monograph, according to the current MEDRA terminology.

Taking into account the possible association between the use of Pelargonium and hepatotoxicity *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix was put on the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs). During the period under review (June 2013 - June 2023), a total of 1097 Individual Case Safety Reports (ICSRs) that occurred during the use of medicinal products containing EPs 7630 were reported spontaneously. After assessment of the data, it was considered that the risk-benefit ratio remained unchanged and positive when used according to the approved terms of the marketing authorisations.

No new information on suspected side effects, exposure during pregnancy and lactation, long-term treatment, off-label use, contraindications, interactions or tolerance was detected which would affect the risk-benefit balance. Other adverse reactions reported with higher disproportionality rate in Eudravigilance (EV) such as gastrointestinal disorders, hypersensitivity reactions, skin and subcutaneous tissue disorders, respiratory disorder were already addressed in the monograph.

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

A European Union list entry is not supported due to lack of adequate published data on genotoxicity.

Annexes

List of references