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Safety and Tolerability of EPs 7630 in Clinical Trials

Heinrich Matthys[1]*, Stephan Köhler[2] and Wolfgang Kamin[3]

[1]Medical Director emeritus, Department of Pneumology, University Hospital Freiburg, Freiburg, Germany
[2]ClQualified Person for Pharmacovigilance, Clinical Research Department, Dr Willmar Schwabe, Karlsruhe, Germany
[3]Clinic for Paediatrics, Evangelic Hospital Hamm, Hamm, Germany

Abstract

Herbal medicines play an increasingly important role in the perception of physicians and patients looking for equally effective, albeit safer approaches to conventional management of certain diseases. The controversy surrounding effective management regimes for respiratory tract infections (RTI) has made many healthcare providers reconsider current therapeutic strategies.

This review presenting the available evidence from clinical trials and non-interventional studies on the safety and tolerability profile of EPs 7630 is based on publications and study reports of 29 clinical trials and post-marketing surveillance studies completed by February 2010. It includes study data from 10,026 adults and children suffering from acute or chronic RTI such as acute tonsillopharyngitis, rhinopharyngitis, sinusitis, bronchitis, or COPD and from 31 healthy subjects.

In 19 double-blind, placebo-controlled trials, the type and incidence rate of adverse events under EPs 7630 were similar to those in patients treated with placebo. For gastrointestinal complaints and epistaxis, event rate differences of 2.9% and of 0.6% against EPs 7630 were determined; hypersensitivity reactions and all other system groups showed rate differences <0.5%. For liver associated events, rate differences of 0.0% for all events and of 0.1% for potentially related events were observed. Patients treated with EPs 7630 did not exhibit increased liver enzyme or bilirubin values – neither in terms of a shift in the mean, nor according to individual deviations from the reference ranges. These findings were fully supported by the data from the post-marketing surveillance studies reviewed.

EPs 7630 appears to be a well-tolerated herbal medicine in the management of RTI in adults and children alike. Evidence for hepatotoxic effects in humans during routine administration was neither provided in the literature, nor by our own analyses.

Keywords: Pelargonium sidoides; Safety; Tolerability; Clinical trials; EPs 7630

Abbreviations: RTI: Respiratory Tract Infection; SmPC: Summary of Product Characteristics; AE: Adverse Event; ADR: Adverse Drug Reaction; C-M-H: Cochran Mantel Haenszel; COPD: Chronic Obstructive Pulmonary Disease; SADR: Serious Adverse Drug Reaction; SAE: Serious Adverse Event; CIOMS: Council for International Organizations of Medical Sciences; ERS: Erythrocyte Sedimentation Rate; ASAT: Aspartate Aminotransferase; ALAT: Alanine Aminotransferase; Plc: Placebo; tid: 3 times daily

Introduction

Respiratory tract infections (RTI) are among the most frequent of all infectious conditions. Taking into consideration that most RTI are of viral origin, the inappropriate use of antibiotics for initial treatment has become an increasingly relevant public health concern because of potential resistance development [1]. Unless an acute tonsillitis accompanied by a group A-β haemolysing streptococci infection or bacterial pneumonia is present, there may not be any need for antibiotic treatment at all [2-4]. Herbal medicines are frequently used to treat RTI; in many cases, however, convincing clinical trial data is lacking. On the other hand, increasing interest in these products on part of patients and physicians underscores the need for such compounds.

EPs 7630* is a herbal drug preparation from the roots of *Pelargonium sidoides* (1:8-10), extraction solvent ethanol 11% [w/w], widely used in Europe, the Commonwealth of Independent States, and Latin America for the treatment of RTI. Several in-vitro-evaluations of EPs 7630 and its isolated constituents have demonstrated pharmacological activities including moderate direct antibacterial and antiviral action and notable immune-modulatory capabilities: immune-modulatory activities are mediated mainly by the release of tumour necrosis factor α and nitric oxides, the stimulation of interferon β, and an increase in natural killer cell activity [5-8]; further biological activities in vitro are improved phagocytosis, oxidative burst and intracellular killing by human peripheral blood phagocytes, and inhibition of interaction between group-A-streptococci and host epithelia [9,10].

Several open-label and randomised double-blind clinical studies have been published over the last years in the indications of tonsillopharyngitis, bronchitis and sinusitis [11-30]. While systematic reviews and meta-analyses of EPs 7630 for acute bronchitis and RTI [31,32] have already shown encouraging evidence from currently available data that EPs 7630 is effective in patients with acute bronchitis, the complete evidence available on clinical tolerability and safety of EPs 7630 has not been presented so far. Recently, a first step to solve this issue was undertaken by Teschke et al. [33,34] who performed in-depth

*EPs® 7630 is the active ingredient in Umckaloabo® (ISO-Arzneimittel, Ettlingen, Germany)

***Corresponding author:** Prof. Dr. Heinrich Matthys, Medical Director emeritus, Department of Pneumology, University Hospital Freiburg, Freiburg, Germany, Tel: +49(0)761-62822; Fax: +49(0)761-6008580; E-mail: hmatthys@t-online.de

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re-evaluations of 32 reports of purported *Pelargonium sidoides* liver function alterations available to the German authorities going back to the year 2004. It was shown that a probable or highly probable causal relationship with *Pelargonium sidoides* could not be assumed in any of the cases, and the authors concluded that convincing evidence is lacking that the herbal drug was a potential hepatotoxin in the analysed cases [33,34].

This review adds to these findings by providing the first overview of safety and tolerability of EPs 7630 based on publications and study reports from clinical trials and post-marketing surveillance studies. According to the current guideline on Summary of Product Characteristics (SmPC) the frequency of adverse reactions should be derived from pooled placebo-controlled studies [35]. Therefore, the review focuses on placebo-controlled clinical pivotal and pilot trials. Available data derived from non-placebo-controlled trials and interaction studies with EPs 7630 are additionally discussed.

Methods

Data Sources

Data reviewed were extracted from publications and unpublished reports of 29 studies investigating the efficacy and tolerability of EPs 7630. They represent all clinical research projects involving EPs 7630 that were funded by the manufacturer and completed by February 2010. Clinical study reports of unpublished trials were provided by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany; they also include pilot studies and hypothesis-generating trials.

Analyses

Incidence rates of adverse events (AEs) were determined separately for each primary study as well as across the studies in an integrated analysis, based on pooled raw data from the primary trials.

In a first step, AEs observed during the analysed studies were classified according to MedDRA Preferred Terms. AEs that were in line with those listed in the SmPC of the marketed product were then assigned to system groups in a second step which reflect adverse drug reactions that may occur seldom (i. e., in 1–10 patients out of 10,000 exposed) or occasionally (i.e., in 1–10 patients out of 1,000 exposed) during treatment with EPs 7630 (gastrointestinal complaints, hypersensitivity reactions, nasal bleeding, gingival bleeding, and liver associated events). An integrated analysis of AEs assigned to the 5 system groups was performed.

Independently of the outcome seen for the integrated analysis, additional analyses of liver enzyme parameters for changes over time were performed, which included ALAT, ASAT, γ GT and serum bilirubin (total, direct, and indirect), in order to further investigate potential hepatotoxic effects of EPs 7630.

The integrated analysis of AEs assigned to the 5 system groups was performed by pooling the data from all 19 placebo-controlled trials available for review. In studies with more than one EPs 7630 dosage level, all patients receiving the herbal drug were pooled. For event rates within the treatment groups, 95% confidence intervals were determined using the Wilson's method (Newcombe method 3) [36]. To compare the relative frequencies of patients with AEs and adverse drug reactions (ADRs) between EPs 7630 and placebo, event risk differences with their 95% confidence intervals were calculated for each system group according to the Newcombe Method 10 [37] and the Cochran-Mantel-Haenszel (C-M-H) test for risk differences between EPs 7630 and placebo were performed. The calculated p-values are to be interpreted in a descriptive manner as no formal hypotheses were prespecified and no adjustment for multiplicity was applied.

Results

Study Designs, Dose Regimens, Number of Patients

Our review includes 19 double-blind placebo-controlled therapeutic studies (Table 1), 1 double-blind placebo-controlled pharmacokinetic interaction study in healthy volunteers, 1 double-blind active-controlled study, 2 open-label active-controlled studies and 6 non-controlled open-label studies. In studies performed in patients the therapeutic indications were acute tonsillopharyngitis, acute sinusitis, acute bronchitis, chronic obstructive pulmonary disease (COPD), acute and

Study, ref	Design[a]	EPs 7630 dose / Patients	Patients with any adverse events	Most common adverse events without assessment of causality[b]	Discontinuations due to adverse events
1[40]	A	**Dose:** Day 1 to 2: 20 drops every hour up to 12 times/day, Day 3 to 10: 20 drops tid **Patients:** 94 children (mean age: 8 ± 1 years)	EPs 10/44 (22.7%) Plc 10/50 (20.0%)	**Acute bronchitis** EPs 2/44 (4.5%); Plc 2/50 (4.0%) **Dry cough** EPs 2/44 (4.5%); Plc 2/50 (4.0%) **Epigastric pain** EPs 1/44 (2.3%); Plc 2/50 (4.0%)	EPs 7/44 (15.9%) Plc 5/50 (10.0%)
2[40]	A	**Dose:** Day 1 to 2: 20 drops every hour up to 12 times/day, Day 3 to 6: 20 drops tid **Patients:** 78 children (mean age: 7 ± 1 years)	EPs 8/40 (20.0%) Plc 8/38 (21.1%)	**Dry cough** EPs 2/40 (5.0%); Plc 6/38 (15.8%) **Rhinitis** EPs 0/40 (0.0%); Plc 4/38 (10.5%)	EPs 2/40 (5.0%) Plc 4/38 (10.5%)
3[40]	A	**Dose:** 20 drops tid for 6 days **Patients:** 124 children (mean age: 8 ± 1 years)	EPs 4/60 (6.7%) Plc 16/64 (25.0%)	**Cough** EPs 1/60 (1.7%); Plc 9/64 (14.1%) **Acute bronchitis** EPs 1/60 (1.7%); Plc 2/64 (3.1%) **Rhinorrhea** EPs 0/60 (0.0%); Plc 3/64 (4.7%)	EPs 4/60 (6.7%) Plc 13/64 (20.3%)
4[13]	A	**Dose:** 20 drops tid for 6 days **Patients:** 143 children (mean age: 8 ± 1 years)	EPs 1/73 (1.4%) Plc 14/70 (20.0%)	**Cough** EPs 0/73 (0.0%); Plc 6/70 (8.6%) **Tracheitis** EPs 1/73 (1.4%); Plc 4/70 (5.7%) **Rhinitis** EPs 1/73 (1.4%); Plc 2/70 (2.9%) **Otitis media** EPs 0/73 (0.0%); Plc 3/70 (4.3%)	EPs 1/73 (1.4%) Plc 11/70 (15.7%)

Study, ref	Design[a]	EPs 7630 dose / Patients	Patients with any adverse events	Most common adverse events without assessment of causality[b]	Discontinuations due to adverse events
5[40]	A	**Dose:** 30 drops tid for 21 days **Patients:** 51 adults (mean age: 40 ± 13 years)	EPs 11/25 (44.0%) Plc 7/26 (26.9%)	**Headache** EPs 5/25 (20.0%); Plc 1/26 (3.8%) **Aggravated cough** EPs 2/25 (8.0%); Plc 0/26 (0.0%)	EPs 9/25 (36.0%) Plc 5/26 (19.2%)
6[40]	A	**Dose:** 60 drops tid for 21 days **Patients:** 272 adults (mean age: 35 ± 11 years)	EPs 5/136 (3.7%) Plc 2/136 (1.5%)	**Gastrointestinal disorders** EPs 5/136 (3.7%); Plc 0/136 (0.0%)	EPs 0/138 (0.0%) Plc 1/136 (0.7%)
7[11]	A	**Dose:** 60 drops tid for 21 days **Patients:** 103 adults (mean age: 35 ± 12 years)	EPs 6/51 (11.8%) Plc 2/52 (3.8%)	**Gastrointestinal disorders** EPs 4/51 (7.8%); Plc 0/52 (0.0%)	EPs 1/51 (1.9%) Plc 0/52 (0.0%)
8[19]	A	**Dose:** 30 drops tid for 7 days **Patients:** 124 adults (mean age: 36 ± 13 years)	EPs 15/64 (23.4%) Plc 10/60 (16.7%)	**Increased ESR** EPs 7/64 (10.9%); Plc 4/60 (6.7%) **Leucocytosis** EPs 3/64 (4.7%); Plc 3/60 (5.0%) **Increased ASAT** EPs 2/64 (3.1%); Plc 1/60 (1.7%) **Increased ALAT** EPs 3/64 (4.7%); Plc 0/60 (0.0%)	None
9[22]	A	**Dose:** 30 drops tid for 7 days **Patients:** 468 adults (mean age: 41 ± 14 years)	EPs 20/233 (8.6%) Plc 16/235 (6.8%)	**Diarrhoea** EPs 1/223 (0.4%); Plc 4/235 (1.7%)	EPs 3/233 (1.3%) Plc 4/235 (1.7%)
10[23]	A	**Dose:** 30 drops tid for 7 days **Patients:** 217 adults (mean age: 37 ± 12 years)	EPs 23/108 (21.3%) Plc 24/109 (22.0%)	**Increased ESR** EPs 10/108 (9.3%); Plc 10/109 (9.2%) **Leucocytosis** EPs 3/108 (2.8%); Plc 4/109 (3.7%) **Increased liver enzymes** EPs 6/108 (5.6%); Plc 4/109 (3.7%)	EPs 3/108 (2.8%) Plc 4/109 (3.7%)
11[40]	B	**Dose:** 30 drops tid for 14 days; 45 drops tid for 14 days **Patients:** 637 adults (mean age: 38 ± 11 years)	EPs (30 drops) 20/214 (9.3%) EPs (45 drops)27/210 (12.9%) Plc 15/213 (7.0%)	**Gastrointestinal disorders** EPs (30 drops) 6/214 (2.8%) EPs (45 drops) 9/210 (4.3%) Plc 6/213 (2.8%) **Respiratory, thoracic and mediastinal disorders** EPs (30 drops) 3/214 (1.4%) EPs (45 drops) 6/210 (2.9%) Plc 3/213 (1.4%) **Epistaxis** EPs (30 drops) 3/214 (1.4%) EPs (45 drops) 4/210 (1.9%) Plc 1/213 (0.5%) **Nervous system disorders** EPs (30 drops) 3/214 (1.4%) EPs (45 drops) 6/210 (2.9%) Plc 0/213 (0.0%)	EPs (30 drops) 5/214 (2.3%) EPs (45 drops) 3/210 (1.4%) Plc 5/213 (2.3%)
12[27]	C	**Dose:** 10 drops tid (children aged 1-6 years) for 7 days; 20 drops tid (children aged >6 to 12 years) for 7 days; 30 drops tid (patients >12 to 18 years) for 7 days **Patients:** 200 children and adolescents (mean age: 10 ± 5 years)	EPs 31/103 (30.1%) Plc 24/97 (24.7%)	**Gastrointestinal disorders** EPs 17/103 (16.5%); Plc 7/97 (7.2%) **Infections and infestations** EPs 5/103 (4.9%); Plc 7/97 (7.2%)	EPs 0/103 (0.0%) Plc 1/97 (1.0%)
13[28]	D	**Dose:** 10 mg, dried,tid for 7 days; 20 mg, dried, tid for 7 days; 30 mg, dried, tid for 7 days; **Patients:** 400 children and adolescents (mean age:13 ± 4 years)	EPs (10 mg) 23/101 (22.8%), EPs (20 mg) 17/99 (17.2%) EPs (30 mg) 19/99 (19.2%) Plc 18/101 (17.8%)	**Gastrointestinal disorders** EPs (10 mg) 9/101 (8.9%) EPs (20 mg) 10/99 (10.1%) EPs (30 mg) 11/99 (11.1%) Plc 11/101 (10.9%) **Infections and infestations** EPs (10 mg) 6/101 (5.9%) EPs (20 mg) 4/99 (4.0%) EPs (30 mg) 2/99 (2.0%) Plc 1/101 (1.0%)	EPs (10 mg) 0/101 (0.0%) EPs (20 mg) 1/99 (1.0%) EPs (30 mg) 1/99 (1.0%) Plc 1/101 (1.0%)

Study, ref	Design[a]	EPs 7630 dose / Patients	Patients with any adverse events	Most common adverse events without assessment of causality[b]	Discontinuations due to adverse events
14[29]	D	**Dose:** 10 mg, dried, tid for 7 days; 20 mg, dried, tid for 7 days; 30 mg, dried, tid for 7 days **Patients:** 406 adults (mean age: 40 ± 13 years)	EPs (10 mg) 18/102 (17.7%) EPs (20 mg) 21/101 (20.8%) EPs (30 mg) 25/101 (24.8%) Plc 11/102 (10.8%).	**Gastrointestinal disorders** EPs (10 mg) 5/102 (4.9%) EPs (20 mg) 9/101 (8.9%) EPs (30 mg) 15/101 (14.9%) Plc 6/102 (5.9%) **Nervous system disorders** EPs (10 mg) 7/102 (6.9%) EPs (20 mg) 7/101 (6.9%) EPs (30 mg) 3/101 (3.0%) Plc 4/102 (3.9%)	EPs (10 mg) 0/102 (0.0%) EPs (20 mg) 0/101 (0.0%) EPs (30 mg) 1/101 (1.0%) Plc 0/102 (0.0%)
15[30]	C	**Dose:** 10 drops tid (children aged 1-6 years) for 7 days; 20 drops tid (children aged >6 to 12 years) for 7 days; 30 drops tid (patients >12-18 years) for 7 days **Patients:** 220 children and adolescents (mean age: 9 ± 5 years)	EPs 2/111 (1.8%) Plc 0/109 (0.0%)	**Gastrointestinal disorders** EPs 1/111 (0.9%); Plc 0/109 (0.0%)	None
16[40]	C	**Dose:** 30 drops tid for 10 days **Patients:** 200 adults (mean age: 37 ± 14 years)	EPs 36/99 (36.4%) Plc 22/101 (21.8%)	**Gastrointestinal disorders** EPs 18/99 (18.2%); Plc 10/101 (9.9%) **Respiratory, thoracic and mediastinal disorders (epistaxis)** EPs 5/99 (5.1%); Plc 6/101 (5.9%) **Nervous system disorders** EPs 5/99 (5.1%); Plc 2/101 (2.0%)	None
17[40]	C	**Dose:** 30 drops tid for 10 days **Patients:** 201 adults (mean age: 45 ± 14 years)	EPs 2/101 (2.0%) Plc 2/100 (2.0%)	**Skin disorders** EPs 2/101 (2.0%); Plc 0/100 (0.0%) **Others** Vascular or hepatobiliary disorder EPs 0/101 (0.0%); Plc 2/100 (2.0%)	None
18[40]	C	**Dose:** 30 drops tid for 10 days; 60 drops tid for 10 days **Patients:** 207 adults (mean age: 36 ± 11 years)	EPs (30 drops) 2/52 (3.8%), EPs (60 drops) 8/52 (15.4%) Plc(30 drops) 1/51 (2.0%) Plc(60 drops) 3/52 (5.8%)	**Gastrointestinal disorders** EPs (30 drops) 0/52 (0.0%) EPs (60 drops) 2/52 (3.8%) Plc (30 drops) 0/51 (0.0%) Plc (60 drops) 1/52 (1.9%) **Respiratory, thoracic and mediastinal disorders** EPs (30 drops) 1/52 (1.9%) EPs (60 drops) 5/52 (9.6%) Plc (30 drops) 0/51 (0.0%) Plc (60 drops) 0/52 (0.0%) **Infections and infestations** EPs (30 drops) 1/52 (1.9%) EPs (60 drops) 1/52 (1.9%) Plc (30 drops) 1/51 (2.0%) Plc (60 drops) 2/52 (3.8%)	EPs (30 drops) 1/52 (1.9%) EPs (60 drops)1/52 (1.9%) Plc (30 drops) 0/51 (0.0%) Plc (60 drops) 1/52 (1.9%)
19[57]	C	**Dose:** 30 drops tid for 24 weeks **Patients:** 200 adults (mean age: 52 ± 10 years)	EPs 51/99 (51.0%) Plc 40/101 (39.6%)	**Gastrointestinal disorders** EPs 16/99 (16.2%); Plc 7/101 (6.9%) **Infections and Infestations** EPs 22/99 (22.2%); Plc 14/101 (13.9%) **Nervous system disorders** EPs 10/99 (10.1%); Plc 4/101 (4.0%)	None

[a]A = Randomised, double-blind, placebo-controlled, parallel-group; B = Randomised, double-blind, placebo-controlled, 4 parallel groups; C = Randomised, double-blind, placebo-controlled; D = Randomised, double-blind, placebo-controlled, dose-finding

[b] Multiple responses per patient possible.

EPs=EPs 7630; ESR=erythrocyte sedimentation rate; ASAT=aspartate aminotransferase; ALAT=alanine aminotransferase; Plc=placebo; tid=3 times daily.

Table 1: Overview of safety and tolerability from placebo-controlled studies.

chronic airway infections, and acute rhinopharyngitis. Eleven studies enrolled only children, 14 studies only adults, and 4 studies enrolled both children and adults.

Across all studies a total of 10,026 patients and 31 healthy subjects were included. Of these, 8,005 individuals were exposed to EPs 7630, 1,883 to placebo, 139 to the comparator acetylcysteine (bronchitis), and 30 to symptomatic therapy not otherwise specified (indication: tonsillopharyngitis). In total, 3,939/10,026 patients (39.3%) were infants, children, or adolescents up to the age of 18 years, of whom 3,243 were exposed to EPs 7630 and 527 to placebo.

In adults and children above 12 years of age, EPs 7630 dose regimens ranged from 30 drops (tonsillopharyngitis, sinusitis, bronchitis, rhinopharyngitis, COPD) to 60 drops thrice daily (sinusitis). In 1 study, 30 drops every hour up to a maximum of 12 times daily for the first 2 days followed by 30 drops thrice daily were administered to adults with sinusitis.

In children ≤ 12 years, EPs 7630 dose regimens included 5 or 10 drops (bronchitis), 10 to 20 drops (tonsillopharyngitis), and 20 drops thrice daily (sinusitis, bronchitis). In 4 studies, 20 drops every hour up to a maximum of 12 times daily for the first 2 days followed by 20 drops

thrice daily were administered for the indications tonsillopharyngitis, sinusitis and bronchitis. In 2dose-finding studies, patients received film-coated tablets with 10 mg, 20 mg or 30 mg EPs 7630 thrice daily.

Overall treatment duration depended on the respective indications and ranged from 6 to 10 days in tonsillopharyngitis (up to 5 weeks in case of recurrent tonsillopharyngitis), 7 to 14 days in bronchitis, 10 days in rhinopharyngitis, 3 to 4 weeks in sinusitis (up to 12 weeks in case of chronic recurrent sinusitis) and 24 weeks in COPD.

Safety and tolerability

No serious adverse drug reactions (SADR) were reported in any of the studies during the treatment period. Overall, 4 serious adverse events (SAEs) were documented (EPs 7630: 3, placebo: 1). All SAEs were assessed as being unrelated to the investigational medication since all events concerned independent infectious diseases (infectious enteritis in 2 cases, 1 case each of diphtheria and pneumonia).

Data from placebo-controlled trials

Overview of individual adverse event and premature withdrawal rates: Table 1 summarises AE information from the 19 double-blind, placebo-controlled trials.

The percentage of patients reporting any AEs (independently of the associated causality assessment) ranged between 1.4% and 51.5% for EPs 7630 and between 0.0% and 39.6% for placebo. In 7 out of the 19 placebo controlled trials both treatment groups showed AE rates of <10% and in 10 trials AE rates of <20% were observed for both groups. AE rates ≥ 25% in any treatment group were observed in studies no. 3, 5, 12, 16, and 19. All studies with AE rates of ≥ 25% in one group were among the 'smaller' trials included in this review, with total sample sizes between 51 and 200 patients. Study no. 19, which exhibited the highest AE rates in both treatment groups, was a long-term trial in COPD, with treatment duration of 24 weeks, whereas all other trials investigated acute conditions and had a period of observation of 3 weeks or less. Due to the substantially longer period of observation the participants of study no. 19 were thus at a higher risk of experiencing at least one AE. As shown in Table 1, the majority of the most frequently reported AEs in double-blind, placebo-controlled trials were among the events included in the SmPC of EPs 7630.

Rates of AE related withdrawals from treatment of 1% or less were observed in 9 out of the 19 placebo-controlled studies for EPs 7630 and in 10 studies for placebo. Fourteen and 12 studies showed withdrawal rates ≤ 2% for EPs 7630 and placebo, respectively. AE related withdrawal rates ≥ 10% in any treatment group were observed in 5 studies (no. 1-5). Out of 14 placebo-controlled trials with any AE-related withdrawals 9 showed lower withdrawal rates in the EPs 7630 group.

Integrated analysis of adverse events across all placebo-controlled trials according to the 5 system groups: Results of the integrated analysis of AEs and ADRs in the 19 placebo-controlled trials focusing on the 5system groups are summarized in Table 2. Data from 4,345 patients (EPs 7630: 2,478; placebo: 1,867) were included in this analysis.

For AEs with any causal relationship to the investigational treatments, significant differences between EPs 7630 and placebo at a descriptive p value level of 5% were detected for AEs in the system groups gastrointestinal complaints (6.0% and 3.1% for EPs 7630 and placebo, respectively; two-sided C-M-H-test p-value: p<0.001), hypersensitivity reactions (0.7% and 0.3%; p=0.036) and epistaxis (1.2% and 0.5%; p=0.028). Further differences in AE rates between placebo and EPs 7630 occurred at the 10% p value level for gingival bleeding (0.2% and 0.0% for EPs 7630 and placebo, respectively; p=0.071).

Regarding potential ADRs, interpretable differences between placebo and EPs 7630 could only be observed for events related to the system groups gastrointestinal complaints (3.6% and 1.8% for EPs 7630 and placebo, respectively; p=0.002) and hypersensitivity reactions (0.4% and 0.1% for EPs 7630 and placebo, respectively; p=0.036). Comparisons in the other system groups revealed no statistically relevant differences between the treatments.

This also holds true for the system group concerning hepatobiliary events: Liver associated AEs (any causality assessment) were reported under EPs 7630 or placebo in 6 out of the 19 placebo-controlled trials. In 4 trials such events were more frequent in patients exposed to EPs 7630 and in 2 trials higher event rates were observed in the placebo group. Across all 19 trials the rates of hepatobiliary AEs were 0.48% for both EPs 7630 and placebo, with a risk difference of 0.00% (95% confidence interval: [0.48%; 0.43%]; p=0.517). Across all trials, 12

System group	Type	EPs 7630 (N=2478)	Placebo (N=1867)	Risk difference
Gastrointestinal complaints	All events	148 (5.97%) [5.11%;6.98%]	57 (3.05%) [2.36%;3.93%]	2.92% [1.68%;4.14%]
	Potentially related events	90 (3.63%) [2.96%;4.44%]	33 (1.77%) [1.26%;2.47%]	1.86% [0.89%;2.82%]
Hypersensitivity reactions	All events	16 (0.65%) [0.40%;1.05%]	5 (0.27%) [0.11%;0.63%]	0.38% [-0.06%;0.81%]
	Potentially related events	9 (0.36%) [0.19%;0.69%]	2 (0.11%) [0.03%;0.39%]	0.26% [-0.07%;0.59%]
Epistaxis	All events	29 (1.17%) [0.82%;1.68%]	10 (0.54%) [0.29%;0.98%]	0.63% [0.06%;1.20%]
	Potentially related events	24 (0.97%) [0.65%;1.44%]	8 (0.43%) [0.22%;0.84%]	0.54% [0.02%;1.05%]
Gingival bleeding	All events	5 (0.20%) [0.09%;0.47%]	0 (0.00%) [0.00%;0.21%]	0.20% [-0.03%;0.47%]
	Potentially related events	5 (0.20%) [0.09%;0.47%]	0 (0.00%) [0.00%;0.21%]	0.20% [-0.03%;0.47%]
Liver associated events	All events	12 (0.48%) [0.28%;0.84%]	9 (0.48%) [0.25%;0.91%]	0.00% [-0.48%;0.43%]
	Potentially related events	5 (0.20%) [0.09%;0.47%]	2 (0.11%) [0.03%;0.39%]	0.09% [-0.21%;0.38%]

Table 2: Incidence of adverse events based on pooled data from double-blind, placebo-controlled trials – number (%) of patients and 95% confidence intervals.

patients exposed to EPs 7630 and 9 patients treated with placebo were affected. Potentially treatment related hepatobiliary AEs were observed in 3 out of the 19 double-blind, placebo-controlled trials, with over-all event rates of 0.20% and 0.11% for EPs 7630 and placebo, respectively (risk difference: 0.09%; 95% confidence interval: [-0.21%; 0.38%]; p=0.266). In 6 out of the 12 hepatobiliary AEs in the EPs 7630 group and in 5 out of the 9 events in the placebo group the patients had abnormal liver enzyme values already at baseline.

Influence on liver enzyme parameters: Although the integrated analysis of adverse events across all placebo-controlled trials revealed no statistically relevant treatment group differences for the system group concerning hepatobiliary events, safety laboratory values were additionally analysed in order to further investigate the purported hepatotoxicity of the herbal drug. ASAT, ALAT, and γ GT were determined in 11 out of the 19 double-blind, placebo-controlled trials (representing a total of 1,578 patients exposed to EPs 7630 and with valid post-treatment values) whereas serum bilirubin was assessed in 3 trials (with 197 evaluable patients treated with EPs 7630 for analysis of total bilirubin and 136 patients for direct and indirect bilirubin). Table 3 shows the number and percentage of patients with values inside the applicable reference range at baseline and elevated values at treatment end, and vice versa. For each parameter the table also presents the average within-group difference between baseline and treatment end. For all parameters except indirect bilirubin, for which only a moderate number of evaluable patients were available, the percentage of study participants treated with EPs 7630 who had normal values at baseline but abnormal values at treatment end was on one level with placebo. Furthermore, the percentage of patients who shifted from normal to abnormal values was always substantially smaller than the percentage of those whose initially abnormal values returned to the reference range at treatment end.

Under both EPs 7630 and placebo treatment, the changes between baseline and treatment end observed in the study groups' mean values were close to zero, indicating that parameter increases and decreases were about evenly distributed among the patients.

Data from Non-Placebo-Controlled Studies and Interaction Studies: This section summarises AE information derived from a placebo-controlled interaction study with EPs 7630 and penicillin V in healthy subjects [38] and from 9 non-placebo-controlled therapeutic studies (3 post-marketing surveillance studies [18,20,21,25,39], 3 open-label outcomes studies [12,16,24], 2 reference-controlled studies versus acetylcysteine [17,40], and a study versus symptomatic treatment [14]), which enrolled a total of 5,527 patients exposed to EPs 7630.

In the therapeutic studies the most frequently reported AEs were gastrointestinal symptoms, e.g. diarrhoea, nausea and epigastric pain, with incidences of up to 1.5% under EPs 7630. The AE rates in the penicillin interaction study in a total of 31 healthy volunteers generally exceeded those in the therapeutic studies; however, AE incidences in the placebo group were higher than in subjects randomised to EPs 7630 (most frequent events: gastrointestinal complaints 13.3% and 62.5%, headache 13.3% and 18.8% of subjects for EPs 7630 and placebo, respectively). No SADRs were reported in any of the studies presented in this section, and the percentage of patients who discontinued their study participation due to an AE did not exceed 3.9%. Furthermore, the results of the interaction study [38] did not indicate any interaction potential between EPs 7630 and penicillin.

Discussion

Our analyses of 29 clinical trials and post-marketing surveillance studies involving a total of more than 8,000 patients exposed to EPs 7630 show that the herbal drug was well tolerated. The favourable safety profile of EPs 7630 is underlined by the fact that no SADRs were reported in this large patient population. AE rates under EPs 7630 were generally somewhat higher in randomised, controlled studies as compared to post-marketing surveillance and open outcomes studies, but this was to be expected which is in line with current literature surveys and reviews [41,42]. In the 19 double-blind, randomized, placebo-controlled trials covered by our review, AEs observed under EPs 7630 and placebo were similar with regard to type and incidence for the majority of system groups or symptoms. Although patients treated with the herbal drug exhibited a slightly higher over-all risk of AEs than those randomised to placebo, there was a higher percentage of AE related withdrawals in the placebo group.

The overview of the results of the placebo-controlled studies shows that the majority of the observed AEs reflect the system groups listed in the SmPC of the marketed products. EPs 7630 was associated with slightly higher incidences of epistaxis, gingival bleeding, hypersensitivity reactions, and gastrointestinal complaints (notably diarrhoea, nausea and epigastric pain). However, the only system group where the risk difference between EPs 7630 and placebo exceeded 1% was gastrointestinal complaints, and the only single event for which an increase by more than 0.5% above the placebo level was observed was epistaxis. These findings are in line with safety results obtained in post-marketing surveillance studies which were conducted in a larger patient population and therefore match most closely the general usage conditions of EPs 7630.

	Baseline normal, post-treatment elevated [a]		Baseline elevated, post-treatment normal [a]		Change between baseline and treatment end	
	EPs 7630	Placebo	EPs 7630	Placebo	EPs 7630	Placebo
ASAT (U/l)	38/1378 (2.8%)	36/1019 (3.5%)	57/212 (26.9%)	47/174 (27.0%)	0.02 ± 15.61 [-0.75; 0.79]	-1.26 ± 12.07 [-1.95; -0.57]
ALAT (U/l)	43/1394 (3.1%)	37/1005 (3.7%)	56/193 (29.0%)	57/180 (31.7%)	0.10 ± 12.30 [-0.51; 0.71]	-0.58 ± 13.01 [-1.32; 0.16]
γGT (U/l)	38/1390 (2.7%)	36/1019 (3.5%)	37/182 (20.3%)	33/160 (20.6%)	0.24 ± 14.19 [-0.46; 0.94]	-0.33 ± 19.66 [-1.46; 0.79]
Bilirubin total (U/l)	6/175 (3.4%)	8/182 (4.4%)	9/20 (45.0%)	7/15 (46.7%)	-0.75 ± 6.61 [-1.69; 0.18]	-0.61 ± 5.41 [-1.37; 0.16]
Bilirubin direct (U/l)	16/116 (13.8%)	9/118 (7.6%)	13/20 (65.0%)	6/18 (33.3%)	0.24 ± 2.94 [-0.26; 0.74]	-0.04 ± 2.14 [-0.40; 0.32]
Bilirubin indirect (U/l)	3/84 (3.6%)	3/96 (3.1%)	3/4 (75.0%)	2/2 (100.0%)	0.63 ± 3.91 [-0.03; 1.30]	-0.21 ± 3.58 [-0.81; 0.40]

[a]Rating compared to the applicable reference range.

Table 3: Liver enzyme values in double-blind, placebo-controlled trials (patients/total and % value, or mean ± SD and 95% confidence interval).

Recently there has been a discussion about suspected, rare hepatotoxic effects of preparations containing *Pelargonium sidoides* extract in the aftermath of the submission of spontaneous reports of hepatobiliary reactions (mostly inflammatory liver diseases and cholestasis) to the competent pharmacovigilance authorities in Germany [43,44]. Considering the fact that *Pelargonium sidoides* extract contains natural coumarin derivatives [45], potential hepatotoxic effects or bleeding complications might give rise to concerns.

However, hepatotoxicity of coumarin (1,2-benzopyrone) is attributed to metabolic activation to an epoxide intermediate, coumarin 3,4-epoxide. Whereas rats are most susceptible to coumarin-induced hepatotoxicity, in most species, particularly in humans, coumarin is predominantly hydroxylated to 7-hydroxycoumarin, a nontoxic metabolite [46-48]. Moreover, coumarin and 7-hydroxycoumarin have been shown to possess antitumour and immunomodulatory effects [49,50]. Since EPs 7630 exclusively contains 7-hydroxycoumarin derivatives, it is not surprising that no pharmacological evidence for hepatotoxicity has been obtained [51]. Likewise, in animal experiments, an influence of EPs 7630 on plasma coagulation, as well as possible pharmacokinetic or pharmacodynamic interactions with warfarin, could be excluded [45]. Moreover, as the 7-hydroxycoumarin derivatives do not possess the structural characteristics required for anticoagulant activity, it appears unlikely that an increased tendency towards bleeding complications arises in patients due to intake of EPs 7630 [45].

Teschke and colleagues [33] performed an in-depth re-evaluation of all reports of purported *Pelargonium sidoides* hepatotoxicity submitted to the German authorities and identified confounding factors like multiple final diagnoses unrelated to *Pelargonium sidoides* as well as poor quality of data and a lack of basic diagnostic measures to exclude even common diseases of the liver in nearly all cases. They determined that according to the criteria proposed by the Council for International Organizations of Medical Sciences (CIOMS) [52] a probable or highly probable causal relationship with *Pelargonium sidoides* could not be assumed in any of the cases and concluded that convincing evidence is lacking that the herbal drug was a potential hepatotoxin in the analysed cases. The results were supported by an in-depth re-evaluation of 13 additional spontaneous reports of suspected hepatotoxicity from which the same conclusions were drawn [34].

The findings of Teschke and colleagues [33,34] are in line with the results of the analyses of data from clinical trials and post-marketing surveillance studies presented in this paper. These analyses revealed neither an incidence of hepatobiliary adverse events in patients exposed to EPs 7630 above the level observed in patients treated with placebo, nor a treatment associated increase of abnormal liver enzyme values or a shift in these safety laboratory parameters' mean values.

The results are also consistent with recently published studies involving the administration of EPs 7630 but not included in our review [53-56] for which no adverse effects on the hepatobiliary system were reported. Current evidence therefore does not provide any evidence that EPs 7630 could have a hepatotoxic effect.

Conclusions

EPs 7630 is a well-tolerated herbal medicine in the management of RTI in children and adults. Evidence for hepatotoxic effects in humans during routine administration was neither provided in the literature, nor by our own analyses.

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Disclosure of conflict of interests

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References

1. Jacobs RF (2000) Judicious use of antibiotics for common pediatric respiratory infections. Pediatr Infect Dis J 19: 938-943.
2. Cooper RJ, Hoffman JR, Bartlett JG, Besser RF, Gonzales R, et al. (2001) Principles of appropriate antibiotic use for acute pharyngitis in adults: background. Ann Intern Med 134: 509-517.
3. Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine; Centers for Disease Control (2001) Principles of appropriate antibiotic use for acute pharyngitis in adults. Ann Intern Med 134: 506-508.
4. Snow V, Mottur-Pilson C, Gonzales R; American College of Physicians-American Society of Internal Medicine; American Academy of Family Physicians; Centers for Disease Control; Infectious Diseases Society of America (2001) Principles of appropriate antibiotic use for treatment of nonspecific upper respiratory tract infections in adults. Ann Intern Med 134: 487-489.
5. Kayser O, Kolodziej H, Kiderlen AF (2001) Immunomodulatory principles of Pelargonium sidoides. Phytother Res 15: 122-126.
6. Kolodziej H (2007) Fascinating metabolic pools of Pelargonium sidoides and Pelargonium reniforme, traditional and phytomedicinal sources of the herbal medicine Phytomedicine 14 (Suppl.6): 9-17.
7. Kolodziej H, Kayser O, Radtke OA, Kiderlen AF, Koch E (2003) Pharmacological profile of extracts of Pelargonium sidoides and their constituents. Phytomedicine 10: 18-24.
8. Kolodziej H, Kiderlen AF (2007) In vitro evaluation of antibacterial and immunomodulatory activities of Pelargonium reniforme, Pelargonium sidoides and the related herbal drug preparation EPs 7630. Phytomedicine 14: 18-26.
9. Conrad A, Hansmann C, Engels I, Daschner FD, Frank U (2007) Extract of Pelargonium sidoides (EPs 7630) improves phagocytosis, oxidative burst, and intracellular killing of human peripheral blood phagocytes in vitro. Phytomedicine 14: 46-51.
10. Conrad A, Jung I, Tioua D, Lallemand C, Carrapatoso F, et al. (2007) Extract of Pelargonium sidoides (EPs 7630) inhibits the interactions of group A-streptococci and host epithelia in vitro. Phytomedicine 14: 52-59.
11. Bachert C, Schapowal A, Kieser M, Malek FA (2006) Treatment of acute bacterial maxillary sinusitis with EPs® 7630-solution: a randomised, double-blind, placebo-controlled trial. Focus Altern Complement Ther 11: 4.
12. Schapowal A, Heger M (2007) EPs® 7630 solution (Umckaloabo®) in the treatment of sinusitis [in German]. Zeitschrift für Phytotherapie 28: 58-65.
13. Bereznoy VV, Riley DS, Wassmer G, Heger M (2003) Efficacy of extract of Pelargonium sidoides in children with acute non-group A beta-hemolytic streptococcus tonsillopharyngitis: a randomized, double-blind, placebo-controlled trial. Altern Ther Health Med 9: 68-79.
14. Blochin B, Heger M (2000) Umckaloabo versus symptomatic therapy in the treatment of acute angina catarrhalis [in German]. Pädiatrie 6: 2-8.
15. Heger M, Bereznoy VV (2002) Tonsillopharyngitis in children not caused by streptococci: Efficacy of an extract from Pelargonium sidoides (EPs 7630) in comparison with placebo [in German]. In: Schulz V, Rietbrock N, Roots I, Loew D (Eds). Phytopharmaka in Forschung und klinischer Anwendung. Steinkopff, Darmstadt 13-25.
16. Bereznoy VV, Heger M, Iljenko LJ, Tischko FA (2009) EPs 7630 solution in adults and children with angina tonsillaris [in German]. Zeitschrift für Phytotherapie 30: 6-13.
17. Blochin B, Haidvogl M, Heger M (1999) Umckaloabo in comparison with acetylcysteine in children with acute bronchitis [in German]. Kassenarzt 39: 46-50.

18. Dome L, Schuster R (1996) Umckaloabo - a phytotherapeutic option for acute bronchitis in childhood? [in German]. Ärztezeitschrift für Naturheilverfahren 37: 216-222.

19. Golovatiouk A, Chuchalin AG (2002) Efficacy of an extract from Pelargonium sidoides (EPs 7630) in comparison with placebo in patients with acute bronchitis [in German]. In: Schulz V, Rietbrock N, Roots I, Loew D (Eds). Phytopharmaka in Forschung und klinischer Anwendung. Vol. VII. Steinkopff, Darmstadt 3-12.

20. Haidvogl M, Heger M (2007) Treatment effect and safety of EPs 7630-solution in acute bronchitis in childhood: report of a multicentre observational study. Phytomedicine 14: 60-64.

21. Haidvogl M, Schuster R, Heger M (1996) Acute bronchitis in childhood. Multicentre study on efficacy and tolerance of the phytotherapeutic preparation Umckaloabo [in German]. Zeitschrift für Phytotherapie 17: 300-313.

22. Matthys H, Eisebitt R, Seith B, Heger M (2003) Efficacy and safety of an extract of Pelargonium sidoides (EPs 7630) in adults with acute bronchitis. A randomised, double-blind, placebo-controlled trial. Phytomedicine 10: 7-17.

23. Matthys H, Heger M (2007) Treatment of acute bronchitis with a liquid herbal drug preparation from Pelargonium sidoides (EPs 7630): a randomised, double-blind, placebo-controlled, multicentre study. Curr Med Res Opin 23: 323-331.

24. Matthys H, Heger M (2007) EPs 7630-solution--an effective therapeutic option in acute and exacerbating bronchitis. Phytomedicine 14: 65-68.

25. Matthys H, Kamin W, Funk P, Heger M (2007) Pelargonium sidoides preparation (EPs 7630) in the treatment of acute bronchitis in adults and children. Phytomedicine 14: 69-73.

26. Chuchalin AG, Berman B, Lehmacher W (2005) Treatment of acute bronchitis in adults with a pelargonium sidoides preparation (EPs 7630): a randomized, double-blind, placebo-controlled trial. Explore (NY) 1: 437-445.

27. Kamin W, Maydannik V, Malek FA, Kieser M (2010) Efficacy and tolerability of EPs 7630 in children and adolescents with acute bronchitis - a randomized, double-blind, placebo-controlled multicenter trial with a herbal drug preparation from Pelargonium sidoides roots. Int J Clin Pharmacol Ther 48: 184-191.

28. Kamin W, Maydannik VG, Malek FA, Kieser M (2010) Efficacy and tolerability of EPs 7630 in patients (aged 6-18 years old) with acute bronchitis. Acta Paediatr 99: 537-543.

29. Matthys H, Lizogub VG, Malek FA, Kieser M (2010) Efficacy and tolerability of EPs 7630 tablets in patients with acute bronchitis: a randomised, double-blind, placebo-controlled dose-finding study with a herbal drug preparation from Pelargonium sidoides. Curr Med Res Opin 26: 1413-1422.

30. Kamin W, Ilyenko LI, Malek FA, Kieser M (2012) Treatment of acute bronchitis with EPs 7630: randomized, controlled trial in children and adolescents. Pediatr Int 54: 219-226.

31. Agbabiaka TB, Guo R, Ernst E (2008) Pelargonium sidoides for acute bronchitis: a systematic review and meta-analysis. Phytomedicine 15: 378-385.

32. Timmer A, Günther J, Rücker G, Motschall E, Antes G, et al. (2008) Pelargonium sidoides extract for acute respiratory tract infections. Cochrane Database of Systematic Reviews: CD006323 pub 2.

33. Teschke R, Frenzel C, Schulze J, Eickhoff A (2012) Spontaneous reports of primarily suspected herbal hepatotoxicity by Pelargonium sidoides: was causality adequately ascertained? Regul Toxicol Pharmacol 63: 1-9.

34. Teschke R, Frenzel C, Wolff A, Herzog J, Glass X, et al. (2012) Â Initially purported hepatotoxicity by Pelargonium sidoides: the dilemma of pharmacovigilance and proposals for improvement. Ann Hepatol 11: 500-512.

35. European Commission (2009) A guideline on summary of product characteristics (SmPC). Revision 2.

36. Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 17: 857-872.

37. Newcombe RG (1998) Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 17: 873-890.

38. Roots I, Arold G, Dienel A, Meng G, Wollny A, et al. (2004) Placebo-controlled, double-blind interaction study with an extract of Pelargonium sidoides und penicillin V in healthy subjects [in German]. Zeitschrift für Phytotherapie 25: 242.

39. Koenig I (1995) From Umckaloabo drug to therapy of respiratory tract infections [in German]. Therapiewoche 45: 1123-1126.

40. Internal report (unpublished), Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe.

41. Hakobyan L, Haaijer-Ruskamp FM, de Zeeuw D, Dobre D, Denig P (2011) Comparing adverse event rates of oral blood glucose-lowering drugs reported by patients and healthcare providers: a post-hoc analysis of observational studies published between 1999 and 2011. Drug Saf 34: 1191-1202.

42. Hakobyan L, Haaijer-Ruskamp FM, de Zeeuw D, Dobre D, Denig P (2011) A review of methods used in assessing non-serious adverse drug events in observational studies among type 2 diabetes mellitus patients. Health Qual Life Outcomes 9: 83.

43. Friemel A, Sachs B (2012) Hepatotoxische Reaktionen im Zusammenhang mit der Anwendung von Pelargonium-haltigen Arzneimitteln. Bulletin zur Arzneimittelsicherheit - Informationen aus BfArM und PEI March: 6-7.

44. Arzneimittelkommission der Deutschen Ärzteschaft (2011) Hepatitis im Zusammenhang mit Umckaloabo® (Aus der UAW-Datenbank. Deutsches Ärzteblatt 108: C1399-C1400.

45. Koch E, Biber A (2007) Treatment of rats with the Pelargonium sidoides extract EPs 7630 has no effect on blood coagulation parameters or on the pharmacokinetics of warfarin. Phytomedicine 14: 40-45.

46. Egan D, O'Kennedy R, Moran E, Cox D, Prosser E, et al. (1990) The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. Drug Metab Rev 22: 503-529.

47. Vassallo JD, Hicks SM, Daston GP, Lehman-McKeeman LD (2004) Metabolic detoxification determines species differences in coumarin-induced hepatotoxicity. Toxicol Sci 80: 249-257.

48. Lake BG (1999) Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment. Food Chem Toxicol 37: 423-453.

49. Stefanova TH, Nikolova NJ, Toshkova RA, Neychev HO (2007) Antitumor and immunomodulatory effect of coumarin and 7-hydroxycoumarin against Sarcoma 180 in mice. J Exp Ther Oncol 6: 107-115.

50. Lacy A, O'Kennedy R (2004) Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. Curr Pharm Des 10: 3797-3811.

51. Loew D, Koch E (2008) Coumarins. A differentiated risk assessment using a herbal medicinal product as an example [in German]. Zeitschrift für Phytotherapie 29: 28-36.

52. Danan G, Benichou C (1993) Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 46: 1323-1330.

53. Kirk KM, Garbes-Netto PG (2007) Post-marketing surveillance of Pelargonium sidoides for treatment of presumably viral acute community acquired tonsillopharyngitis [in Spanish]. Revista Panamericana de Infectología 9: 15-24.

54. Luna LA Jr, Bachi AL, Novaes e Brito RR, Eid RG, Suguri VM, et al. (2011) Immune responses induced by Pelargonium sidoides extract in serum and nasal mucosa of athletes after exhaustive exercise: modulation of secretory IgA, IL-6 and IL-15. Phytomedicine 18: 303-308.

55. Patiroglu T, Tunc A, Eke Gungor H, Unal E (2012) The efficacy of Pelargonium sidoides in the treatment of upper respiratory tract infections in children with transient hypogammaglobulinemia of infancy. Phytomedicine 19: 958-961.

56. Marquís M, González Yibirín M, Barreto B (2011) Evaluación de la efectividad del Renikan (extracto del Pelargonium sidoides estandarizado EPs® 7630) en el tratamiento de las infecciones de las vías respiratorias superiores de etiología viral. Archivos Venezolanos de Farmacologia y Terapeutica 30: 79-85.

57. Matthys H, Pliskevich DA, Bondarchuk OM, Malek FA, Tribanek M, et al. (2013) Randomised, double-blind, placebo-controlled trial of EPs 7630 in adults with COPD. Respir Med 107: 691-701.