# Public Assessment Report
# for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

# EPs® 7630 syrup[1]
# (Pelargonium Sirup ENR. 2170149/ Umckaloabo Saft für Kinder ENR. 2170150/ Pelargonium-Schwabe Bronchialsaft für Kinder ENR. 2170151)
# Pelargonium sidoides root liquid extraction preparation (DER 1 : 8-10), dried*, extraction solvent: ethanol 11 % (w/w)

***1 part of the dried preparation is equivalent to 6.25 – 12.5 parts (w/w) of herbal substance.**
**(Resulting of drying the Pelargonium sidoides root liquid extraction preparation (DER 1 : 8-10), extraction solvent: ethanol 11 % (w/w))**
**[Declaration of the extracts as stated by the MAH. Currently subject of leagal procedings in Germany.]**

## DE/W/102/pdWS/001

## Marketing Authorisation Holder:
## Dr. Willmar Schwabe GmbH & Co. KG

| | |
|---|---|
| **Rapporteur:** | Germany (DE) |
| **Finalisation procedure (day 120)** | **12.07.2016** |
| **Date of finalisation of PAR:** | **07.10.2016** |

**ADMINISTRATIVE INFORMATION**

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|---|---|
| Invented name of the medicinal product: | Pelargonium Syrup |
| INN (or common name) of the active substance(s): | In the liquid:<br>Pelargonium sidoides root liquid extraction preparation (1 : 8-10),<br>Extraction solvent: Ethanol 11 % (w/w).<br>(Pelargonium sidoides extract EPs® 7630)<br>In the syrup:<br>Pelargonium sidoides root liquid extraction preparation (1 : 8-10), dried*<br>Extraction solvent: Ethanol 11 % (w/w).<br><br>*1 part of the dried preparation is equivalent to 6.25 – 12.5 parts (w/w) of herbal substance. |
| MAH: | Dr. Willmar Schwabe GmbH & Co. KG |
| Currently approved Indication(s) | Pelargonium Sirup is indicated in symptomatic treatment of acute bronchitis |
| Pharmaco-therapeutic group (ATC Code): | Cough and cold preparations, expectorants<br>R05C |
| Pharmaceutical form(s) and strength(s): | <u>EPs® 7630 Syrup</u><br>100 g (= 93.985 ml) syrup contains) Pelargonium sidoides root liquid extraction preparation (1 : 8-10), dried* 0.2506 g<br>extraction solvent: ethanol 11% (w/w).<br>The dried herbal preparation was prepared by drying/eliminating the ethanol of the Pelargonium sidoides root liquid extraction preparation (1 : 8-10) extraction solvent: ethanol 11% (w/w).<br>*1 part of the dried preparation is equivalent to 6.25 – 12.5 parts (w/w) of herbal substance.<br><br><u>EPs® 7630 solution</u><br>10 g (9.75 ml) of the investigational medicinal product contain 8 g Pelargonium sidoides root liquid extraction preparation (DER 1:8-10) extraction solvent: ethanol 11% (m/m). |

# I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

# II. RECOMMENDATION

Assessment of this study within a Type II variation procedure did not lead to a change of SmPC and PL. No changes are proposed in this procedure.

# III. INTRODUCTION

As required by the German authority (BfArM) the pediatric study no. 701003.01.010 was conducted to confirm safety and tolerability of Pelargonium Sirup ENR. 2170149/ Umckaloabo Saft für Kinder ENR. 2170150/ Pelargonium-Schwabe Bronchialsaft für Kinder ENR. 2170151) in children (Post authorisation study).

On 7th April 2016, the MAH submitted a completed paediatric study for Pelargonium Sirup, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has been provided and a study report of 15.July 2013.
The MAH stated that the submitted paediatric study does not influence the benefit risk for Pelargonium syrup and that there is no consequential regulatory action.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the study(ies)

In the submitted study an oral solution and oral syrup were used.

1. Umckaloabo Lösung (Zul. Nr. 61899629.00.00) contains the active substance EPs® 7630, an ethanol-containing extract in the pharmaceutical form of solution. It was authorised in Germany for children from 1 to 18 years on 10.12.2005. In the clinical study this formulation is called “EPs® 7630 solution”.

2. Three identical preparations (Pelargonium Sirup ENR. 2170149; Umckaloabo Saft für Kinder ENR. 2170150 and Pelargonium-Schwabe Bronchialsaft für Kinder ENR. 2170151) contain a dry Pelargonium extract prepared from the EPs® 7630 ethanol-containing extract by eliminating the ethanol, and in the pharmaceutical formulation as syrup. They were authorised for children from 1 to 18 years on 13.10.2010. In the clinical study this formulation is called “EPs® 7630 syrup”.

## IV.2 Clinical aspects

### 1. Introduction

The MAH submitted a final report(s) for a prospective, multi-centre, randomised safety study of Pelargonium sidoides extract EPs® 7630 in children (1 to 5 years old) suffering from acute bronchitis. Two different pharmaceutical formulations with an ethanol-containing and ethanol-free pelargonium extract were compared.

### 2. Clinical study

**Study No. 701003.01.010**

Title: Safety and tolerability of Pelargonium sidoides extract EPs® 7630 in children (1 to 5 years old) suffering from acute bronchitis.
A prospective, multi-centre, randomised safety study

- **Description**
- **Methods**
  - **Objective(s)**

Primary objective:
The primary objective of the clinical trial was to evaluate the safety and tolerability of a treatment with EPs® 7630 syrup in comparison to EPs® 7630 solution in patients between 1 and 5 years old suffering from acute bronchitis.

Secondary objectives:
During the study course the patients' health status was also assessed.

- **Study design**

The study was conducted as a prospective, randomised, multi-centre study in Germany. Included were patients from 1 year to 5 years old suffering from symptoms related to acute bronchitis. The patients had at least two of the three bronchitis-relevant symptoms, i.e. coughing, pulmonary rales at auscultation, and dyspnoea and the start of symptoms ≤ 72 hours prior to inclusion into the study. The individual treatment period was one week (day 0 visit 1; a reconsultation visit on day 7 visit 2). Patients with suspected or diagnosed pneumonia, rhinosinusitis, otitis media, or GABHS tonsillo-pharyngitis were not included in the study.

The clinical examination includes the severity assessment of the three bronchitis specific symptoms (i.e. coughing, pulmonary rales at auscultation, and dyspnoea) and other respiratory tract infection symptoms (as nasal discharge, congestion of pharyngeal mucosa, nasal congestion, sneezing, hoarseness, conjunctivitis, diarrhea, restlessness, loss of appetite, vomiting, sleep disorder) using a 5-point-rating scale, body temperature measurement, vital signs (heart rate and respiratory rate measurement) and general physical examination.

The Integrative Medicine Patient Satisfaction Scale (IMPSS) was used at visit 2 to describe the patient´s satisfaction with the treatment (very satisfied, satisfied, neutral, dissatisfied, very dissatisfied). The Integrative Medicine Outcomes Scale (IMOS) was used to describe the general health status of the patient (Complete recovery, major improvement, slight to moderate improvement, no change, deterioration).

- **Study population /Sample size**

602 patients were randomized to the syrup or solution group. 411 patients were randomized to syrup and 191 patients were randomized to solution. At least one third of the included patients were between 1 and 3 years old.

- **Number of subjects included in the analysis:**

| Treatment group | Planned to be randomised | Randomised | Patients taken into account for the analysis | | |
|---|---|---|---|---|---|
| | | | Safety | Efficacy | |
| | | | Safety set | Full analysis set | Per protocol set |
| EPs® 7630 syrup | 400 | 411 | 403 | 403 | 370 |
| EPs® 7630 solution | 200 | 191 | 188 | 188 | 155 |
| All | 600 | 602 | 591 | 591 | 525 |

- **Treatments**

The EPs® 7630 solution used in the present clinical study is a liquid herbal drug preparation from the roots of Pelargonium sidoides (herbal drug: extract ratio 1:8-10); extraction solvent: ethanol 11% (w/w). 10 g of the investigational medicinal product contain 8 g EPs® 7630.

The EPs® 7630 syrup used in the present clinical study is a liquid herbal drug preparation from the roots of Pelargonium sidoides (herbal drug: extract ratio 1:8-10); extraction solvent: ethanol 11% (w/w). 100 g of the investigational medicinal product contain 0.2506 g dried extract.

The administered doses were
Syrup: 2.5 ml three times daily
Solution: 10 drops three times daily
The mean treatment duration of all patients was 7.63 ± 1.01 days and was comparable in both groups (EPs® 7630 syrup: 7.63 ± 0.96 days; EPs® 7630 solution: 7.79 ± 1.09 days).

Assessor´s comment:
The dosages used in the clinical study correspond to the dosages approved for children.

- **Outcomes/endpoints**

The primary aim of the study was to obtain information about the safety of a 7-day treatment.

**Safety analysis:**
The safety was examined by the frequency, severity and nature of adverse events, changes in vital signs and changes in laboratory values.

**Efficacy analysis:**
The patient's health status was examined in changes in individual respiratory tract infection symptoms related to acute bronchitis as well as the total symptoms score, treatment outcome using the Integrative Medicine Outcomes Score (IMOS) and satisfaction with the treatment using the Integrative Medicine Patient Satisfaction Scale (IMPSS) as assessed by the legal representatives of the patients.

- **Statistical Methods**

Since this study was a randomized open-label safety-study no hypothesis was formulated and the data were analyzed in an exploratory way. Accordingly, all two-sided p-values resulting from any statistical test or model were interpreted in a descriptive manner. The adverse events were tabulated, absolute and relative frequencies of the system organ classes were given. Furthermore, data were summarized for clinical laboratory tests and vital signs.

➢ **Results**

Date of report: 15 July 2013

- Recruitment/ Number analysed

| | EPs 7630 syrup | EPs 7630 solution |
|---|---|---|
| Screened: n=602 | | |
| Randomised: n=602 | | |
| Treatment<br>Without any intake of medication | n=411<br>n=8 | n=191<br>n=3 |
| Treatment phase | n=403 | n=188 |
| Analysis: Safety analysis set | n=403 | n=188 |
| Full analysis set<br>Relevant protocol violations*<br>Treatment compliance<br>Visit schedule/med. intake<br>Prior/concom. medication<br>Drop out | n=403<br>n=33<br>n=20<br>n=4<br>n=5<br>n=5 | n=188<br>n=33<br>n=24<br>n=4<br>n=2<br>n=5 |

* multiple reasons possible

- **Baseline data**

A total of 316 (53.5%) patients were boys and 275 (46.5%) were girls. The ratio of female and male children was similar in both treatment groups. Patients were on average 3.01 ± 1.35 years old, had a mean height of 99.1 ± 11.9 cm and a mean weight of 15.8 ± 3.9 kg. At baseline the mean of the three individual symptoms coughing, pulmonary rales at auscultation and dyspnoea and their total score were similar in both treatment groups (total score: EPs® 7630 syrup: 5.67 ± 2.07 points; EPs® 7630 solution: 5.62 ± 2.04 points).

The occurrence of vomiting since the start of respiratory tract infection symptoms before inclusion into the study was documented separately. The number of patients with vomiting before study inclusion was comparable, but slightly higher in patients allocated to the syrup group [EPs® 7630 syrup: 37/403 (9.2%); EPs® 7630 solution: 14/188 (7.5%)].

- **Efficacy results**

The mean decrease in individual as well as total bronchitis-specific symptoms scores coughing, pulmonary rales at auscultation, and dyspnoea from Baseline to Day 7 was similar in the EPs®-7630-treatment-groups (decrease in total score: EPs® 7630 syrup: -4.25 ± 2.17 points; EPs® 7630 solution: -4.24 ± 2.12 points; two-sided t-test: p=0.974)
The remission and improvement rates of individual bronchitis-specific symptoms coughing, pulmonary rales at auscultation, and dyspnoea from Baseline to Day 7 were more than 90% for each symptom and comparable in both treatment groups (EPs® 7630 syrup: coughing: 91.8%, pulmonary rales at auscultation: 94.5%, dyspnoea: 95.0%; EPs® 7630 solution: coughing: 92.5%, pulmonary rales at auscultation: 93.5%, dyspnoea: 96.3%)

Each further bronchitis-associated respiratory tract infection symptom (nasal discharge, congestion of pharyngeal mucosa, sneezing, conjunctivitis, restlessness, loss of appetite, vomiting, and sleep disorder) showed a more or less pronounced decrease from Baseline to Day 7 and was comparably distributed in both EPs®-7630-treatment-groups.

The Integrative Medicine Outcomes Scale (IMOS) assessed at visit 2, showed in about 80% of the patients of both EPs®-7630-treatment-groups the general health status had completely recovered or improved to a major extent on Day 7.

The results of the Integrative Medicine Patient Satisfaction Scale (IMPSS) were similar in both treatment groups. The legal representatives of the patients were very satisfied or satisfied with the treatment in more than 85% of the patients in both treatment groups.

**Assessor's comment:**
The efficacy results doesn´t hint to any differences between the syrup and solution treatment. However, because of general methodological reasons, this study was an open-label safety study, no placebo control group, not blinded, self-limiting disease, the results have to be interpreted with caution and cannot prove efficacy.

- **Safety results**

Eleven children (8 of EPs® 7630 syrup / 3 of EPs® 7630 solution) were drop-outs without any intake of the investigational product. The remaining 591 patients received the investigational product at least once (EPs® 7630 syrup: 403 patients, EPs® 7630 solution: 188 patients) and were included in the safety analysis (safety analysis set, SAF).
Four participants terminated the study with a reason of an adverse event (EPs® 7630 syrup: 4 patients, EPs® 7630 solution: 0 patient). The reasons of premature discontinuation were angina tonsillaris, otitis media, pneumonia and bronchopneumonia.

During the study period a total of 66 AEs was observed in 57/403 patients (14.1%) in the EPs®-7630-syrup-group and a total of 37 AEs in 31/188 patients (16.5%) in the EPs®-7630-solution-group. Patients in both groups showed mostly mild or moderate adverse events. The distribution of AEs according to the SOCs involved was similar with no major difference between the age subgroups 1-3 years and 4-5 years of both treatment-groups. In both groups the causality of most AEs was assessed as 'not related' (syrup: 62/66 AEs (94.0%); solution: 29/37 AEs (78.4%). Except one case (diarrhoea) with the assessment 'possible' the causality of all other AEs was assessed as unlikely..

One serious adverse event (head injury caused by an iron rod) occurred during the study which was assessed as 'not related' to the investigational product.

**Adverse events potentially related to study medication**
Potentially treatment related adverse events were 4/403 (1.0%) patients in the syrup group and 7/188 (3.7%) patients in the solution group.

In the syrup group 4/66 (6.1%) potentially treatment related events were ALT/AST increase in 2 patients, AST increase 1 patient and in 1 ADR in the SOC 'gastrointestinal disorders' (diarrhoea).

In the solution-group 8/37 AEs in 7 patients (21.6%) were potentially treatment related: 1 ADR hepatic enzyme increased, 2 ADRs aspartate aminotransferase increased and 1 ADR transaminase increased (ALT/AST/ Gamma-GT increase: 2 patients, AST increase: 2 patients) and 4 of 8 ADRs in 3 patients within the SOC 'gastrointestinal disorders' (diarrhoea: 2 ADRs; vomiting: 1 ADR; upper abdominal pain: 1 ADR).

Of the 382 EPs®-7630-syrup-patients who had a normal value of ALT at Baseline, 6 (1.6%) patients showed an increase above ULN (higher values) at the end of treatment. In 4 of the 6 patients the ALT increase at study end was clinically not relevant, in the remaining 2 patients the marginal increase was assessed as clinically relevant and documented as an adverse event (ALT in patient no. 10803: 48 U/l, patient no. 11111: 37 U/l, reference range: 5-36 U/l).

Out of 14 patients with increased ALT values at Baseline, 10 (71.4%) patients showed normal values at the end of treatment.

In the analysis of the total EPs®-7630-solution-group out of 183 patients with normal ALT values at Baseline, 4 (2.2%) patients showed a higher value at the end of treatment. In two of the 4 patients the ALT increase was clinically not relevant, in 2 patients the increase was clinically relevant and had been documented as an AE (ALT in patient no. 13130: 79 U/l, patient no. 14406: 62 U/l, reference range: 5-36 U/l). In one patient who had an elevated ALT value at Baseline, the measurements at the end of the study showed a value within the reference range again.

A clinically relevant deviation of a liver enzyme value at end of treatment visit not present at baseline had to be documented as an AE.
One patient with three increased liver values at Day 7 already had an increased AST measurement at Baseline. In none of the children the elevated liver values expressed any clinical symptoms. Liver-associated AEs occurred with an overall rate of 1.2% (7/591) patients in both EPs®-7630-treatment-groups. As the rate is lower than the corresponding frequency within the general population (8-11%), especially as those elevations are correlated with respiratory infections (Berg, 2009) the relationship was assessed as unlikely.

The occurrence of vomiting between Baseline and Day 7 was additionally documented and assessed. In 22/403 (5.5%) patients of the EPs®-7630-syrup-group and 11/188 (5.9%) patients in the EPs®-7630-solution-group vomiting occurred between Baseline and Day 7. The percentage of vomiting between Baseline and Day 7 was comparable in both treatment groups and even lower compared to baseline (37/403 (9.2%) patients of the syrup and 14/188 (7.5%) of the solution group).

An integrated analysis of adverse events from historical data of three studies in children with acute bronchitis (Kamin et al. 2010, Kamin et al. 2012 and Matthys et al. 2007) and the current study assigned to the 4 terms (gastrointestinal complaints, hypersensitivity reactions, nasal and gingival bleeding, and liver associated events) listed in the SmPCs of the marketed products was performed. No relevant statistical differences in the number of AEs or ADRs between the two application forms could be observed, neither in the current study nor in the integrated analysis of the pooled data.

**Assessor's comment:**
Currently, the following information is given among adverse drug reaction in the SmPC:

1. Uncommon gastrointestinal complaints as epigastric discomfort, heartburn, nausea, diarrhoea, (gelegentlich Magen-Darm-Beschwerden wie Magenschmerzen, Sodbrennen, Übelkeit oder Durchfall)
2. Rare mild nasal and gingival bleeding (selten leichtes Zahnfleisch- oder Nasenbluten).
3. Rare hypersensitivity reactions as exanthema, urticaria, pruritus of the skin (In seltenen Fällen Überempfindlichkeitsreaktionen (Exanthem, Urtikaria, Pruritus an Haut und Schleimhäuten).
4. Very rare severe allergic reactions as swelling oft the face, dyspnoe, decreased blood pressure (sehr selten schwere Überempfindlichkeitsreaktionen mit Gesichtsschwellung, Dyspnoe und Blutdruckabfall).
5. Frequency not known: Liver dysfunction (Fälle von Leberschäden und Hepatitis wurden im Zusammenhang mit der Einnahme von Pelargonium-haltigen Arzneimitteln berichtet; die Häufigkeit ist nicht bekannt.)

6. Uncommon increased increased liver enzyme values (Gelegentlich Erhöhungen der *Leberwerte)*
7. Frequency not known: Decrease of thrombocytes (Erniedrigungen der Thrombozyten, Häufigkeit nicht bekannt. Diese können auch durch die Grunderkrankung bedingt sein.)

Increased liver enzyme

The argument of the applicant, as the rate is lower than the corresponding frequency within the general population (8-11%), especially as those elevations are correlated with respiratory infections (Berg, 2009) the relationship was assessed as unlikely, can not be accepted completely, as in the paediatric population the general rate can not be estimated as high as in adults. The Baseline data show that 15 (2,53%) of 591 (403 and 188) paediatric patients with acute bronchitis had increased ALT values, what is a lower frequency than within the general population (8-11%). In the course of the one week treatment new cases developed and parallel also cases normalized. At Day 7, the end of the study, the number of patients with increased values was comparable with Baseline. As the ADR is labelled, no additional activities are concluded from the results of this study.

Gastrointestinal complaints

In 22/403 (5.5%) patients of the EPs®-7630-syrup-group and 11/188 (5.9%) vomiting occurred and was assessed as unrelated to the study medication. The percentage of vomiting between Baseline and Day 7 was lower compared to baseline in this study. From historical data gastrointestinal complaints are known for pelargonium preparations and are labelled with a frequency of "uncommon". No new frequency can be concluded from the study results for the ethanol-free syrup.

**3. Discussion on clinical aspects**

The results of the submitted open-label study suggest, there are no differences in efficacy between EPs®-7630-solution (that contains as active substance the ethanol-containing EPs® 7630 fluid extract) and EPs®-7630-syrup containing an ethanol-free dry extract, prepared from the same EPs® 7630 ethanol-containing extract by eliminating the ethanol. However, open label studies should generally be interpreted with caution and cannot proof efficacy.

The adverse event profile resulting from the study is in line with the known safety profile of Pelargonium preparations. There were no relevant differences in safety results between the ethanol-containing solution and ethanol-free syrup. From general safety aspects regarding ethanol, the ethanol-free syrup should be the preferred pharmaceutical formulation for the use in children. The relationship of the increased liver enzymes to the products was considered unrelated, but the causal association cannot completely be ruled out.
Because of safety reasons the use in children from 1 to 6 years was only accepted under the condition of the supervision of a doctor. This safety advise is considered necessary and should be maintained.

# V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted results of the open-label clinical safety study does not change the benefit-risk assessment of pelargonium syrup. The proposal of no SmPC and PL changes by the applicant is accepted.

- **Recommendation**

No further action required.