



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Pelargonium sidoides* DC; *Pelargonium reniforme* Curt., radix as released for public consultation on 15 October 2023 until 15 January 2024.

	Organisations and/or individuals
1	Schwabe Dr. Willmar Schwabe GmbH & Co. KG, Willmar-Schwabe-Str. 4, D-76227 Karlsruhe, Germany Angela Müller, Head Global Regulatory Affairs angela.mueller@schwabe-group.com +49 721 4005 9512

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Table 2: Discussion of comments

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.2. Posology and method of administration	Schwabe	<p>General Comment We appreciate the inclusion of the paediatric group of children from 3 to 5 years of age into the target population which is in line with the broad long-standing safe therapeutic use of Pelargonium root extract over 30 years in the EU and with safety data from > 1600 children from 3 to 5 years from the clinical development programme, which included also non-comparative open label studies and a large safety study [Kamin et al., 2018; Zimmermann, 2019 unpublished; Kamin et al., 2023]. Such comprehensive data is above standard among herbal medicines for acute respiratory tract infections in children [Längler et al., 2019; Wopker et al., 2020].</p>	
4.2. Posology and method of administration	Schwabe	<p>Current wording: Herbal preparation a) Adolescents over the age of 12 years, adults and elderly Single dose: <u>1.4 ml</u>, 3 times daily Daily dose: <u>4.2 ml</u> Children between 6-12 years Single dose: <u>0.9 ml</u>, 3 times daily Daily dose: <u>2.7 ml</u> Children between 3 and 5 years Single dose: 0.4 ml, 3-times daily Daily dose: 1.2 ml</p> <p>Proposal for revision Herbal preparation a)</p>	<p>Not endorsed.</p> <p>Coming from the posology for the German product (1976) and several other products on the market (see table 1 of AR): <u>1 ml=21 drops</u></p> <p>Adults and adolescents over 12 years: 3 times daily 30 drops= 1.4 ml Children 6-12 years: 3 times daily 20 drops=0.9 ml</p>

Section number and heading	Interested party	Comment and Rationale	Outcome
		<p>Adolescents over the age of 12 years, adults and elderly Single dose: <u>1.2 ml liquid extract</u>, 3-times daily Daily dose: <u>3.6 ml liquid extract</u></p> <p>Children between 6-12 years Single dose: <u>0.8 ml liquid extract</u>, 3-times daily Daily dose: <u>2.4 ml liquid extract</u></p> <p>Children between 3 and 5 years Single dose: <u>0.4 ml liquid extract</u>, 3-times daily Daily dose: <u>1.2 ml liquid extract</u></p> <p>Rationale In the posology of herbal preparation a), liquid extract and finished product were partly mixed up. Proposal is made to adapt the posology to be in line with the dosages of approved medicinal products in Europe.</p>	<p>Children 1-5 years: 3 times daily 10 drops= 0.4 ml</p>
4.8. Undesirable effects	Schwabe	<p>Current wording: <i>Hepatobiliary disorders: Hepatotoxicity, hepatitis. The frequency is not known.</i></p> <p>Proposal for revision <i>Hepatobiliary disorders: Liver disorders. The frequency is not known.</i></p> <p>Rationale Hepatitis was added to the section describing possible side effects of Pelargonium extract. As discussed on page 71 of the drafted HMPC Assessment Report, there is no evidence that Pelargonium extract is a hepatotoxic agent. Initially it was based on a series of cases, for which other causes are possible. It is unclear why this leads to the conclusion that the side effects section is extended by adding hepatitis.</p> <p>Virally induced acute respiratory infections lead to hepatic involvement and elevated hepatic enzyme activity. During a research project in six paediatric</p>	Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		<p>practices and one hospital, a prospective study was carried out with the aim of investigating the prevalence of hepatic involvement in connection with respiratory tract infections [<i>Kamin et al., 2022</i>]. Patients between 1–18 years of age with symptoms of an acute respiratory tract infection were recruited. There was one visit at the start of the study and a further visit after 3 to 7 days. Blood samples for laboratory tests (AST, ALT, γ-GT, AP, bilirubin, serum protein) were taken during both visits. A total of 1010 children and adolescents were enrolled in the research project between January 2014 and December 2016. Of these, 936 also took part in the second visit. The analysis showed that the activity of the hepatic enzymes (AST, ALT, γ-GT) is elevated in a substantial proportion of the children and adolescents with an acute respiratory tract infection: 8.6% on visit 1, 9.2% on visit 2. This demonstrates for the first time that the underlying disease acute respiratory infection also affects the liver to a certain extent and can explain the observed increase in liver enzyme activity. Out of 992 study participants, 373 (37.6%) had at least one previous medication during the last 30 days prior to study inclusion. Most frequent were analgesic or antiphlogistic drugs [<i>Kamin et al., 2022</i>].</p> <p>In order to enhance the readability and understandability of the labelling in the patient information leaflet or SmPC, we suggest replacing the term <i>hepatotoxicity</i> by the MedDRA preferred term <i>liver disorders</i>.</p>	

References

- Kamin W, Adams O, Kardos P, Matthys H, Meister N, Strassburg CP.** Liver involvement in acute respiratory infections in children and adolescents – results of a non-interventional study. *Front Pediatr.* **2022**; 10:840008.
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- Längler A, Zuzak TJ, Fricke O, Seifert G.** Pflanzliche Arzneimittel in der Pädiatrie [Herbal medicines in paediatrics]. *Monatsschrift Kinderheilkunde.* **2019**; 167(9):768-777. English translation provided by MAH.
- Wopker PM, Schwermer M, Sommer S, Längler A, Fetz K, Ostermann T, Zuzak TJ.** Complementary and alternative medicine in the treatment of acute bronchitis in children: A systematic review. *Complement Ther Med.* **2020**; 49:102217.
- Zimmermann A.** AE analyses according to age classes and SmPC system groups for clinical trials including children and adolescents. Summary of results. **2019.** Internal report, unpublished.