European Journal of Pediatrics (2023) 182:2453–2454
https://doi.org/10.1007/s00431-023-04877-6

CORRESPONDENCE

Letter to the Editor, regarding Li L, Zhu X, Chen X, Gao J, Ding C, et al. Advances in targeted therapy for pulmonary arterial hypertension in children. Eur J Pediatr. 2022 Dec 17

Maurice Beghetti[1] · Dunbar Ivy[2] · Nicola Scott[3] · Sandra Machlitt-Northen[3] · Mary Ann Lukas[3]

Received: 3 February 2023 / Revised: 7 February 2023 / Accepted: 13 February 2023 / Published online: 27 February 2023
© The Author(s) 2023

We congratulate Li and colleagues on their comprehensive review on pulmonary arterial hypertension (PAH) therapy advances in children [1]. However, we note with concern that information provided on Volibris (ambrisentan) in Table 1 is not current for the European Union (EU) and Japan, with potential safety/dosing implications. Firstly, under "approved use," it states "off-label" for ambrisentan, whereas regulatory approval was obtained in 2021 (September for the EU and April for Japan).

This is particularly important because the approved age is only from 8 to < 18 years, which is not detailed in the manuscript and the dosing information in the table does not reflect approved recommendations for dosing by weight [2]. The approval for ambrisentan only covers children weighing ≥ 20 kg with initial dosing of 2.5 mg (for which a tablet strength is now available), and up-titration dependent on clinical response and tolerability to 5 mg for children < 35 kg, or initial dose of 5 mg for weights ≥ 35 kg, with up-titration to 7.5 mg for 35 to < 50 kg, and to 10 mg for ≥ 50 kg. These data are based on the randomized clinical trial conducted by Ivy et al. [3], which is also referenced in the recent ESC/ERS guideline PAH update [4]. Lower dosing is recommended with cyclosporine A coadministration [2]. Lastly, safety and efficacy have not been established in patients under 8 years; hence, use in these patients is not recommended and as described in the EU product information [2], and by Laffan et al. [5], there may also be potential risk for ambrisentan in children < 4 years based on preclinical data in juvenile rats.

We hope this important corrective information is well received and that an updated version reflecting these updates will be published to provide practitioners with the appropriate and approved approach to ambrisentan use in children with PAH.

Authors' contributions Mary Ann Lukas, Nicola Scott, and Sandra Machlitt-Northen wrote the main text of the letter. All authors reviewed and agreed to the letter text.

Availability of data and materials Not applicable.

Declarations

Ethical approval Not applicable.

Competing interests For Dunbar Ivy, the University of Colorado contracts with GSK, Actelion, Eli Lilly, and United Therapeutics to be a consultant. Maurice Beghetti reports remunerations for lectures and/or consultancy from Actelion, Bayer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline (GSK), Merck Sharp & Dohme, and Pfizer and unrestricted research grants from Actelion and Bayer. Mary Ann Lukas, Nicola Scott, and Sandra Machlitt-Northen are employees of GSK and hold shareholder status in the company.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

This comment refers to the article available online at https://doi.org/10.1007/s00431-022-04750-y.

✉ Mary Ann Lukas
mary.ann.lukas@gsk.com

[1] Centre Universitaire de Cardiologie et Chirurgie Cardiaque Pédiatrique, Congenital Heart Center (CHUV et HUG), Geneva, Switzerland

[2] University of Colorado School of Medicine Children's Hospital Colorado, Aurora, CO, USA

[3] GlaxoSmithKline, Brentford, UK

References

1. Li L, Zhu X, Chen X, Gao J, Ding C et al (2022) Advances in targeted therapy for pulmonary arterial hypertension in children. Eur J Pediatr
2. Volibris Product Information https://www.ema.europa.eu/en/documents/product-information/volibris-epar-product-information_en.pdf. Accessed 12 Jan 2023
3. Ivy D, Beghetti M, Juaneda-Simian E et al (2020) A randomized study of safety and efficacy of two doses of ambrisentan to treat pulmonary arterial hypertension in pediatric patients aged 8 years up to 18 years. J Pediatr X 5:100055
4. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, ESC/ERS Scientific Document Group et al (2023) 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 61(1):2200879
5. Laffan S, Kohrs L, Kambara T, Rambo M, Jucker B et al (2019) Brain weight effect of ambrisentan in juvenile rats associated with breathing sounds, apnea and sustained hypoxemia. Presented at the 59th Teratology Society Annual Meeting, San Diego, CA

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.