To:

Head of Paediatric Medicines
European Medicines Agency

Notification of discontinuation of a paediatric development which is covered by an agreed PIP Decision

Actives substances(s): Bumetanide

Invented name: N/A

Latest Decision number(s): 1) P/0340/2021

Corresponding PIP number(s): 1) EMEA-001303-PIP01-12

Date of initial marketing authorisation granted: N/A

Date of authorisation of new indication, pharmaceutical form or route of administration: N/A

Please note that development of the medicinal product above in the following **condition(s)/indication(s)**:

Autistic Spectrum Disorder

☒ has been discontinued

☐ has been suspended/put on long-term hold (with possible re-start at a later time)

for the following reason(s): (tick all that apply)

☐ (possible) lack of efficacy in adults

☐ (possible) lack of efficacy in children

☐ (possible) unsatisfactory safety profile in adults

☐ (possible) unsatisfactory safety profile in children

☐ commercial reasons (please specify:)

☐ manufacturing / quality problems

☐ other regulatory action (please specify:) (e.g. suspension, revocation of M.A.)

☐ other reason (please specify:)

Please add a brief description (max 2000 characters) of the reason(s) for the discontinuation / suspension:

The Sponsor, Institut de Recherches Internationales Servier (I.R.I.S.), has decided to definitely discontinue the following pivotal studies conducted with bumetanide (S95008):

- CL3-95008-001 entitled "Efficacy and safety of bumetanide oral liquid formulation in children and adolescents aged from 7 to less than 18 years old with Autism Spectrum Disorder. A 6-month

randomised, double-blind, placebo controlled multicentre parallel group study to evaluate efficacy and safety of bumetanide 0.5mg twice a day followed by an open label active 6-month treatment period with bumetanide (0.5mg twice a day) and a 6 weeks discontinuation period after treatment stop".

- CL3-95008-002 entitled "Efficacy and safety of bumetanide oral liquid formulation in children aged from 2 to less than 7 years old with Autism Spectrum Disorder. A 6-month randomised, double-blind, placebo controlled multicenter parallel group study to evaluate efficacy and safety of bumetanide 0.5mg twice a day followed by an open label active 6-month treatment period with bumetanide (0.5mg twice a day) and a 6 weeks discontinuation period after treatment stop".

This decision was based on the recent results of the two studies and upon the assessment of the benefit/risk ratio (B/R) of the treatment with bumetanide in the targeted population. None of the efficacy endpoints (CARS, SRS, CGI, Vineland) were reached after 6 months of treatment neither in children and adolescents aged from 7 to less than 18 years, nor in children aged from 2 to less than 7 years. As no benefit has been identified to treat ASD paediatric patients with bumetanide, the B/R of the study treatment in this indication is now considered negative, due to the identified risk of hypokalaemia and associated effects linked to the drug's diuretic activity.

This decision is not related to unexpected safety concerns.

Please note that if the PIP has been submitted as part of a marketing authorisation application in order to comply with the requirements of Article 7 of the Paediatric Regulation (as a condition of the validation of the respective application) and a marketing authorisation was granted based on this application, then there is a legal obligation to complete that PIP. The same applies if there has been a successful post-authorisation application, where the PIP was included in order to comply with the requirements of Article 8 of the Paediatric Regulation.

Please confirm if any of the above applies to the PIP in question:

Yes ☐ No ☒

If yes, it means that based on the Marketing Authorisation obtained at the end of that initial procedure or the successful post-authorisation application, as applicable, you are obliged to complete that PIP. That obligation cannot be cancelled by a unilateral decision, including by withdrawing the MA. Such PIP must be completed, unless it is modified in agreement with the PDCO by removing all outstanding PIP measures or granting a full product-specific waiver instead (upon relevant circumstances in accordance with the Paediatric Regulation). Non-completion of a binding PIP establishes noncompliance with the requirements of the Paediatric Regulation, which the European Medicines Agency has an obligation to report to the European Commission.

Name and signature of the PIP contact point:	Signature on file
Date:	7 September 2021
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