MHRA
10 South Colonnade
Canary Wharf
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United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

agree a paediatric investigation plan and grant a deferral and grant a waiver

MHRA-100594-PIP02-22

Scope of the Application

Active Substance(s)

N-[4-(6-fluoro-3,4-dihydro-1H-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide; Azetukalner

Condition(s)

Treatment of primary generalised tonic-clonic seizures, Treatment of epilepsy syndromes

Pharmaceutical Form(s)

Capsule, hard Age-appropriate liquid formulation

Route(s) of Administration

ORAL USE

Name / Corporate name of the PIP applicant

Xenon Pharmaceuticals Inc.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Xenon Pharmaceuticals Inc. submitted to the licensing authority on 28/11/2022 13:44 GMT an application for a Paediatric Investigation Plan

The procedure started on 06/11/2023 15:04 GMT

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to agree a paediatric investigation plan and grant a deferral and grant a waiver

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This decision is forwarded to the applicant, together with its annex and appendix.

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Final Decision Letter

MHRA-100594-PIP02-22

Of 12/12/2025 17:49 GMT

On the adopted decision for Azetukalner (MHRA-100594-PIP02-22) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on a paediatric investigation plan

This decision applies to a Paediatric Investigation Plan for Azetukalner, Capsule, hard Age-appropriate liquid formulation , ORAL USE .

This decision is addressed to Xenon Pharmaceuticals Inc., 200-3650 Gilmore Way, Burnaby, BC, CANADA, V5G 4W8

ANNEX I

1. Waiver

1.1 Condition:

Condition 1: Treatment of primary generalised tonic-clonic seizures The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than one month of age Pharmaceutical form(s): Capsule, hard Age-appropriate liquid formulation Route(s) of administration: ORAL USE Reason for granting waiver: on the grounds that the specific medicinal product is likely to be unsafe. Condition 2: Treatment of epilepsy syndromes The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than one month of age Pharmaceutical form(s): Capsule, hard Age-appropriate liquid formulation Route(s) of administration: ORAL USE Reason for granting waiver: on the grounds that the specific medicinal product is likely to be unsafe. Reason for Refusing Waiver: Not Applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Condition 1: Treatment of primary generalised tonic-clonic seizures Condition 2: Treatment of epilepsy syndromes

2.2 Indication(s) targeted by the PIP:

Condition 1: Treatment of primary generalised tonic-clonic seizures Condition 2: Treatment of epilepsy syndromes

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

For both conditions: The paediatric population from 1 month to less than 18 years of age

2.4 Pharmaceutical Form(s):

For both conditions: Capsule, hard Age-appropriate oral liquid formulation

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	1	Study 1 (CMC01) (same study for both conditions) Development of an age-appropriate oral liquid dosage form for use in paediatric patients from 1 month of age.
Non-Clinical Studies	1	Study 2 (NS02) (same study for both conditions) Juvenile animal study to support the evaluation of safety of azetukalner when used in paediatric population from 1 month to less than 18 years of age.
Clinical Studies	5	Study 3 (XPF-010-303, X-ACKT) measure for the treatment of primary generalised tonic-clonic seizures only) Double-blind, randomised, placebo controlled trial to evaluate efficacy, safety, and tolerability of azetukalner as adjunctive treatment in participants from 12 years to less than 18 years of age (and adults) diagnosed with primary generalised tonic-clonic seizures (PGTCS) and to contribute to modelling of the exposures in children below 12 years of age with PGTCS. Study 4 (CES-01) (same study for both conditions) Open-label study to

		evaluate the PK, safety, activity and tolerability of azetukalner in sequential cohorts of paediatric patients from 2 years to less than 18 years of age diagnosed with an epilepsy syndrome or PGTCS, and to contribute to modelling of exposures in children with epilepsy syndromes and PGTCS. Study 5 (CES-02) (same study for both conditions) Open-label study to evaluate the PK, safety, activity and tolerability of azetukalner in sequential cohorts of paediatric patients from 1 month to less than 2 years of age diagnosed with epilepsy syndromes and to contribute to modelling of exposures in children with epilepsy syndromes and PGTCS. Study 6 (CES-OLE) (same study for both conditions) Long-term open-label study to evaluate safety, activity and tolerability of azetukalner in paediatric patients from 1 month to less than 18 years of age diagnosed with PGTCS or epilepsy syndromes who completed studies CES-01 and CES-02. Study 7 (CES-04) (study for treatment of epilepsy syndromes only) Confirmatory study to evaluate safety and efficacy of azetukalner in treatment of epilepsy syndromes identified in Study 6 (CES-OLE). Key elements of this study, including its design, to be agreed with the PDCO by December 2035.
Extrapolation, Modeling & Simulation Studies	3	Study 8 (MES-01) (same study for both conditions) Population PK (popPK) study to confirm or modify the dose of azetukalner in treatment of PGTCS based on data from adults and paediatric patients. Study 9 (MES-02) (same study for both conditions) Physiologically-based model (PB-PK) to predict and confirm or modify the dose of azetukalner compared to the regimen used in the studies in adults and PIP Study 3 for children from 1 month to less than 2 years of age. Extrapolation Plan (measure for the treatment of primary generalised tonic-clonic seizures only) Studies

		3 (XPF-010-303), 4 (CES-01) and 8 (MES-01), are part of the extrapolation plan of efficacy data from adults and adolescents to the paediatric population from 2 years to less than 12 years of age with PGTCS.
Other Studies	0	Not applicable.
Other Measures	0	Not applicable.

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	31/12/2037
Deferral of one or more studies contained in the paediatric investigation plan:	Yes