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Chugai Receives Approvals for Additional Indication of Evrysdi in Pre-Symptomatic Spinal Muscular Atrophy (SMA) and Additional Dosage for SMA Infants Under 2 Months of Age

- As the only approved oral drug for Spinal Muscular Atrophy (SMA), Evrysdi is expected to contribute to earlier treatment, including for people with pre-symptomatic SMA and those under 2 months of age
- Approval based on the overseas Phase II RAINBOWFISH study demonstrating Evrysdi's efficacy and safety in pre-symptomatic SMA infants (up to 6 weeks of age at first dose)

TOKYO, September 24, 2024 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced that the Ministry of Health, Labour and Welfare (MHLW) has approved today "Evrysdi® Dry Syrup 60 mg" (generic name: risdiplam) for an additional indication of pre-symptomatic spinal muscular atrophy (SMA) predicted by genetic testing, and an additional dosage for patients under 2 months of age. Evrysdi received orphan drug designation from MHLW for "spinal muscular atrophy" in March 2019, and the application for additional indication and dosage were approved under priority review.

"We are very pleased that with this approval, we can now deliver Evrysdi to people with SMA of all ages after birth, regardless of symptom onset. As the only oral treatment for SMA, Evrysdi has been helping many people with SMA and their families. SMA treatment is expected to maximize its effect when intervention begins at an earlier stage. We are confident that this approval will allow Evrysdi to contribute even more to SMA treatment" said Chugai's President and CEO, Dr. Osamu Okuda.

This approval is based on the results of the overseas Phase II RAINBOWFISH study, for pre-symptomatic SMA infants (up to 6 weeks of age at first dose) diagnosed genetically with SMA. The RAINBOWFISH study included infants with two or more copies of the *SMN2* gene. Generally, the lower the number, the more severe the disease.[1]

In SMA, the loss of motor neurons may begin before symptoms start,[2,3] so initiating treatment early is critical for better outcomes, and newborn screening plays an important role for early diagnosis. Evrysdi is expected to provide high medical value by enabling immediate treatment after diagnosis, regardless of symptom onset.

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[Electronic Package Insert Information] ※Underlined parts were changed and added

Indications: Spinal muscular atrophy

Dosage and Administration:

For patients less than 2 months of age, the usual dosage is 0.15 mg/kg risdiplam administered orally once a day after a meal.

For patients 2 months to less than 2 years of age, the usual dosage is 0.2 mg/kg risdiplam administered orally once a day after a meal.

For patients older than 2 years of age, the usual dosage for patients weighing less than 20 kg is 0.25 mg/kg risdiplam and for patients weighing 20 kg or more is 5 mg risdiplam administered orally once a day after a meal.

(Note) Regarding the indication, following the revision of the diagnostic criteria for designated intractable diseases in April 2024, the underlined part was added, but with this approval for additional indication, the underlined part has been deleted.

"Spinal muscular atrophy (excluding those predicted to develop by genetic testing)"

[Reference Information]

Majority of newborn babies with spinal muscular atrophy (SMA) treated with Roche's Evrysdi able to sit independently after 1 year of treatment (Press release by Roche issued on October 4, 2023)
https://www.roche.com/media/releases/med-cor-2023-10-04

Chugai Files for Additional Indication of Evrysdi for Pre-Symptomatic Spinal Muscular Atrophy and Additional Dosage for Infants up to 2 Months of Age (Press release on February 15, 2024)
https://www.chugai-pharm.co.jp/english/news/detail/20240215150000_1046.html

About the RAINBOWFISH study

The RAINBOWFISH study [NCT03779334] is an open-label, single-arm, multicentre study, investigating the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in babies (n=26), from birth to six weeks of age (at first dose) with genetically diagnosed SMA who are not yet presenting with symptoms. The primary endpoint was the proportion of infants in the primary efficacy population who are sitting without support for at least 5 seconds at month 12 assessed by the BSID-III (Bayley Scales of Infant and Toddler Development - Third Edition) gross motor scale. Japan is not included in this study.

About Evrysdi

Evrysdi is a survival motor neuron 2 (*SMN2*) splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Evrysdi is designed to treat SMA by increasing and sustaining the production of the survival motor neuron (SMN) protein. SMN protein is found throughout the body and is critical for maintaining healthy motor neurons and movement. Evrysdi was approved in the U.S. in August 2020, in Europe in March 2021, and in Japan in June 2021. In Japan, it has now received approval for an additional indication in pre-symptomatic SMA and an additional dosage for infants under 2 months of age.

Additionally, an application for the addition of a tablet formulation (for patients 2 years of age and older weighing 20 kg or more) was submitted in April 2024 as a new treatment option. If approved, the tablet

formulation will allow for storage and transport at room temperature and eliminate the need for measuring doses, leading to more convenient storage and administration, enabling contribution for treatment choices that suit individual conditions and lifestyles.

About spinal muscular atrophy (SMA)[4]

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease that causes muscule atrophy and muscle weakness due to degeneration of the motor neuron.[5] The causative gene for SMA is the survival motor neuron (*SMN*) gene. The disease develops because of insufficient production of functional SMN protein from *SMN2* gene alone, in addition to the dysfunction of the *SMN1* gene.[6]

Source:

1. Yamamoto T, et al. Brain Dev. 2014; 36: 914-20.
2. Kolb SJ, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017 Dec;82(6):883-891.
3. Govoni A, et al. Time Is Motor Neuron: Therapeutic Window and Its Correlation with Pathogenetic Mechanisms in Spinal Muscular Atrophy. Mol Neurobiol. 2018 Aug;55(8):6307-6318.
4. With your SMA. Walking with everyone involved in spinal muscular atrophy (SMA). Available from: https://with-your-sma.jp/. Accessed August 2024. (Japanese only)
5. Farrar MA and Kiernan MC. The genetics of spinal muscular atrophy: progress and challenges. Neurotherapeutics. 2015;12:290-302.
6. Kolb SJ and Kissel JT. Spinal muscular atrophy. Neurol Clin. 2015;33:831-46.

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