No. 19-83

November 20, 2019
Eisai Co., Ltd.

PARKINSON'S DISEASE TREATMENT
EQUFINA® 50MG TABLETS (SAFINAMIDE MESILATE) LAUNCHED IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has launched the Equfina® 50mg TABLETS (safinamide mesilate, "Equfina") for the indication of improvement of wearing-off phenomenon in patients with Parkinson's disease under treatment with a drug containing levodopa in Japan. Manufacturing and marketing approval of Equfina were obtained on September 20, 2019, and Equfina was included to Japan's National Health Insurance Drug Price List on November 19, 2019.

Equfina, developed by Meiji Seika Pharma Co., Ltd. (Headquarters: Tokyo, "Meiji") in Japan, is a once-daily oral treatment for Parkinson's disease, and is selective and reversible monoamine oxidase B (MAO-B) inhibitor helping to maintain the density of endogenous dopamine and exogenous dopamine from levodopa-containing drugs in the brain (dopaminergic mechanism). In addition, Equfina blocks voltage-dependent sodium ion channels and inhibits glutamate release (non-dopaminergic mechanism). In the Japanese clinical studies for Parkinson's disease patient under treatment with a drug containing levodopa, the extension of levodopa's duration of effect ("on" time) of one hour or more and improvement of motor functions were shown. The improvement effect of the wearing off phenomenon is expected.

This approval is based on a double-blind, placebo-controlled Phase II/III study (study ME2125-3) to evaluate the efficacy and safety of Equfina as add-on therapy as well as an open label Phase III study (study ME2125-4) to evaluate the safety and efficacy of long-term administration of Equfina in Japanese patients with Parkinson's disease with wearing-off phenomena who are currently receiving levodopa.
In the study ME2125-3, with regard to the change in mean daily "on" time from baseline to 24 weeks of the treatment phase with Equfina (50 mg and 100 mg), the "on" time showed the statistically significant increases compared to placebo-controlled treatment (50mg of Equfina: 1.39 hours extension (95%CI: 0.67, 2.11, P=0.0002), 100mg of Equfina: 1.66 hours extension (95%CI: 0.93, 2.39, p<0.0001)). The most

common adverse drug reactions (ADRs) (incidence 3% and higher) observed with patients with Equfina were dyskinesia and visual hallucination.
In the study ME2125-4, with regard to the change (Least Square Mean (LSM) ± Standard Deviation of Lateral Position (SDLP)) in mean daily “on” time from baseline to 52 weeks of the treatment phase, the “on” time with long-term administration of Equfina (50mg and 100mg) was extended (1.42±2.72 hours), and showed the continued effectiveness. The most common ADRs (incidence 3% and higher) observed with patients with Equfina were dyskinesia, falls, and constipation.

There are approximately 200,000 patients suffering from Parkinson’s disease in Japan,[1] and the number of patients is increasing due to the aging of the population.[1,2] Drugs containing levodopa are widely used to treat Parkinson’s disease by replenishing the brain’s supply of dopamine. However, as the disease progresses, the “on” time decreases, and there are cases where the patients may experience wearing-off phenomenon, a return of Parkinson’s disease symptoms before the next dose. Decrease of “on” time which effects on the opportunity for work and daily activities for patients with Parkinson’s disease is a major factor to lower the quality of life (QOL).

In Japan, Meiji holds the manufacturing and marketing approval for Equfina, and Eisai exclusively sells Equfina. With providing Equfina as a new option for Parkinson’s disease treatment in Japan, Eisai will make further contribution to improve the patients’ QOL and to create the daily energetic lives of patients’ families, by increasing the time that Parkinson’s disease patients can freely be active on their own will.

Media Inquiries	Healthcare Professionals Inquiries (available in Japanese only)
Eisai Co., Ltd. Public Relations Department +81-(0)3-3817-5120	Eisai *hhc* Hotline 0120-419-497 (Contact hours: Weekdays 9:00 – 18:00, Weekends and Public holidays: 9:00 – 17:00, 365 days a year) 24-hour support system by Chatbot (AI Hotline) https://medical.eisai.jp/inquiry/chat/product.html For Equfina:

<Notes to editors>

1. About “Equfina® 50mg TABLETS” (generic name: safinamide mesilate)

[Product Outline]

Brand name:	Equfina® 50mg TABLETS
Dosage form:	A film-coated white tablet containing 65.88mg of safinamide mesilate (50mg as safinamide) in a tablet
Indication:	Improvement of wearing-off phenomenon in patients with Parkinson’s disease under treatment with a drug containing levodopa
Dosage and administration:	This medicine is used in combination with a drug containing levodopa. In general for adults, 50 mg of safinamide is orally administered once a day. In addition, 100 mg can be orally administered once a day according to the symptoms.
National Health Insurance (NHI) Drug Price:	¥963.90 per tablet of Equfina® 50mg TABLETS
Date of marketing approval:	September 20, 2019
Listing in NHI Drug Price List:	November 19, 2019
Manufacturer and distributor:	Meiji Seika Pharma Co., Ltd.
Distributor:	Eisai Co., Ltd.

Safinamide mesilate, discovered and developed by Newron Pharmaceuticals S.p.A. (Headquarters: Milan, Italy), is a selective monoamine oxidase B (MAO-B) inhibitor, which reduces the degradation of excreted dopamine, helping to maintain the density of dopamine in the brain. Additionally, safinamide mesilate blocks sodium ion channels and inhibits glutamate release, and possesses both dopaminergic and non-dopaminergic mechanisms.

Global and domestic clinical studies of Equfina in combination with levodopa for the treatment of mid- to late-stage Parkinson's disease showed extended “on” time and an improvement in motor function.[3,4]

Safinamide mesilate is marketed under the name “Xadago” in 15 countries in Europe, the United States and Australia, and under the name “Onstryv” in Canada.

2. About Licensing Agreement between Eisai and Meiji for Safinamide Mesilate

In 2011, Meiji granted exclusive rights to develop, manufacture and commercialize the drug in Japan and Asia. Under the license agreement signed between Eisai and Meiji in March 2017, Eisai has the exclusive rights to market Equfina in Japan, as well as to develop and market Equfina in Asia*.

* South Korea, Taiwan, Brunei, Cambodia, Laos, Malaysia, the Philippines, Indonesia, Thailand, Vietnam, Myanmar, Singapore, Hong Kong, and Macau

3. About Parkinson’s Disease

Parkinson's disease is a neurodegenerative disease that causes motor impairment such as shaking in the limbs, muscular rigidity and shuffling gait, as well as non-motor impairment such as sensation impairment with pain, insomnia, and autonomic failure. It is caused by degeneration of the dopamine nervous system, which leads to a shortage of dopamine, a neurotransmitter in the brain. According to the estimation of Japanese Society of Neurology, there are approximately 200,000 patients suffering from Parkinson’s disease in Japan.[1] Also, the approximate 3 million patients suffer from Parkinson’s disease in Asia.[5] The number of patients is increasing due to the aging of the population.[2] Levodopa is widely used to treat Parkinson's disease by replenishing the brain's supply of dopamine. However, as the disease progresses, the duration of a drug containing levodopa of effect (“on” time) decreases,

and there are cases of Parkinson's disease symptoms returning before the next dose (“wearing-off” phenomenon). To prevent the “wearing-off” phenomenon, combination therapy with a drug that has a different mechanism of action to a drug containing levodopa is administered.

4. About study ME2125-3 (Phase II/III Clinical Study)

Study ME2125-3 was a multicenter, double-blind, placebo-controlled, randomized, parallel group study to evaluate the efficacy and safety of two doses of safinamide (50 and 100 mg, once a day for 24 weeks) administered orally as add-on therapy in Japanese patients with Parkinson's disease with wearing-off phenomenon who are currently receiving a drug containing levodopa. In this study, the primary endpoint was the change in mean daily “on” time from baseline to 24 weeks of the treatment phase, and verified the superiority of each dose of safinamide over placebo. Regarding the change in mean daily “on” time from baseline to 24 weeks of the treatment phase with Equfina 50 mg and 100 mg, the “on” time showed the statistically significant increases compared to placebo-controlled treatment (50mg of Equfina: 1.39 hours increase (95%CI: 0.67, 2.11), 100mg of Equfina: 1.66 hours increase (95%CI: 0.93, 2.39)). The ADR incidence rates in this study were 24.8% for placebo, 31.6% for Equfina 50mg, and 30.3% for Equfina 100mg. The most common ADRs (incidence 3% and higher) observed with patients with Equfina were dyskinesia and visual hallucination.

5. About study ME2125-4 (Phase III Clinical Study)

Study ME2125-4 was an open-label, multicenter study to evaluate the long-term efficacy and safety of two doses of safinamide (50 and 100 mg, once a day for 52 weeks) administered orally as add-on therapy in Japanese patients with Parkinson’s disease with wearing-off phenomenon who are currently receiving a drug containing levodopa. In this study, in addition to evaluating the safety of long-term administration of safinamide, the study evaluated the change in mean daily “on” time from baseline to 52 weeks of the treatment phase as the primary efficacy endpoint. Regarding the changes (LSM ± SDLP) from baseline of mean daily “on” time of 52 weeks of treatment, it was 1.42±2.72 hours, and the continuous efficacy of long-term administration was shown. The ADR incidence rate was 38.9% for Equfina. The most common ADRs (incidence 3% and higher) observed were dyskinesia, falls, and constipation.

[1] Japanese Society of Neurology. Treatment and Management Guideline 2018 for Parkinson’s Disease

[2] Japan Intractable Diseases Information Center http://www.nanbyou.or.jp/

[3] Borgohain R et al. Randomized Trial of Safinamide Add-On to Levodopa in Parkinson's Disease With Motor Fluctuations. *Mov Disord.* 2014 Feb;29(2):229-37

[4] Schapira AH et al. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. *JAMA Neurol.* 2017 Feb 1;74(2):216-224

[5] E Ray Dorsey et al. Global, regional, and national burden of Parkinson’s disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016 *Lancet Neurol.* 2018;17:939–53