AEGERION PHARMACEUTICALS K.K.

AEGERION PHARMACEUTICALS K.K.—a Japanese subsidiary of Aegerion Pharmaceuticals Inc., a U.S. pharmaceutical company that specializes in the development and commercialization of innovative therapies for rare diseases—released an oral drug in December 2016 that features a new mechanism of action for homozygous familial hypercholesterolemia (HoFH). This drug raises hopes of alleviating the burden on Japanese patients suffering from this rare disease.

On December 15, 2016, AEGERION PHARMACEUTICALS K.K. ("Aegerion") launched a HoFH drug, "Juxtapid capsules 5mg", "Juxtapid capsules 10mg", and "Juxtapid capsules 20mg" (The generic name of which is Lomitapide Mesilate)("*Juxtapid*").

HoFH is a rare genetic lipid disorder resulting in very high levels of low-density lipoprotein cholesterol (LDL-C) so-called "bad cholesterol." Patients with HoFH have a reduced ability to remove LDL-C from the bloodstream which results in very high LDL-C levels. Having just made its market debut, Juxtapid is indicated to treat HoFH patients in Japan.

***Juxtapid* is a drug that has been approved in Japan as an oral medicine for HoFH.**

Establishment of the Japanese subsidiary; compassion for patients in Japan

Aegerion Pharmaceuticals Inc., the head office of Aegerion, was established in Cambridge, Massachusetts, U.S.A in 2005. Its proprietary drug, Lomitapide, was approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in December 2012 and July 2013, respectively. As of April 2016, Lomitapide was approved in 38 countries around the world. Hoping to deliver the same medicine as early as possible to Japanese patients suffering from the same disease, and to meet the unmet medical needs, Aegerion Pharmaceuticals Inc. set up its Japanese subsidiary in September 2013 in Minato Ward, Tokyo.

Ms. Masako Nakamura, Representative Director of Aegerion K.K. ("Ms. Nakamura") explains that most of therapies for rare diseases are approved in North America and Europe first. "I felt the situation dissatisfying where the patients in Japan were always lagging behind in having a therapy that had been approved in the U.S. and Europe first." For this reason, she began to think of obtaining drug approval as expeditiously as possible in Japan.

While studying to enter the Japanese market with a strong motivation, she was encouraged by the enforcement of *The Act on Medical Care for Intractable Disease Patients* which included HoFH as one of the rare diseases designated for medical treatment grants. Realizing that this act would reduce the medical expenses borne by patients, Ms. Nakamura began to research the Japanese market to examine the possibility of business development in Japan. Ms. Nakamura states, "The system of reducing the burden on patients who have rare diseases is unique to Japan, which I think is admirable."

As a result of the market research, Japan had the second largest market, following the U.S., in terms of the number of patients who are afflicted by HoFH. It was also discovered that the Japanese patients did not have any sufficient therapies, hence, an unmet medical need. Given these facts, Aegerion Pharmaceuticals Inc. decided to establish its Japanese subsidiary.

Ms. Masako Nakamura, Representative Director of Aegerion K.K.

The changing Japanese pharmaceutical market and orphan drugs

The Japanese pharmaceutical market is changing dramatically now. There are a great number of systems emerging attractive to companies dealing in orphan drugs, the medicines for rare diseases.

Previously, some critics said that Japan did not have pharmaceutical products on its market that had already been on sale in other countries. They also pointed out that it took much longer in Japan than in other countries until the review of a drug approval application was completed and the product came onto the market. This "drug lag" issue, however, has gradually been resolved by the government's initiatives.

Ms. Nakamura talked about the current situation in the changing Japanese pharmaceutical market based on her own experience. "The Japanese procedures for drug approval are clear. Although some complain that the Japanese approval procedures are obscure and slow, I have found them to be more efficient than those in other countries by actually having gone through the process. Particularly, the process for orphan drugs is lucid, with the Japanese authorities designating the review period as nine months. As a matter of fact, it only took 8.8 months for *Juxtapid* to obtain approval. In other countries, the process would not have been accomplished so smoothly. I think we can say the "drug lag" issue in Japan has been resolved. "

Juxtapid was designated as an orphan drug in September 2013 and then went through a Phase III clinical trial in Japan. The application for the marketing authorization was submitted in January 2016, and then *Juxtapid* was approved in September 2016. This means that it took only 8.8 months after the application was submitted.

In Japan, designation as an orphan drug enables a pharmaceutical company manufacturing such a drug to receive a grant from the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIONH). It also has other benefits, such as deduction of part of the tax incurred corresponding to development expenses*. This system is unique to Japan, and Ms. Nakamura has found it highly beneficial. She emphasizes this point, saying, "Every company investing in orphan drugs should fully research orphan drug policy and the benefits for rare disease patients."

*The research and development promotion system for rare-disease drugs (orphan drugs)

Numerous supporters

After *Juxtapid* was approved, pricing negotiations with the authorities also went very smoothly. In Japan, drugs need to be priced within 60 days in principle, or no later than 90 days, after being approved. On this point, Ms. Nakamura says, "There are seldom other

countries that require prices to be fixed within 90 days. In Europe, it could take up to several years for the price & reimbursement to be determined even after the drug is approved." In addition to the well-established and easy-to-understand system for drug pricing, what impressed Ms. Nakamura was the cooperative attitude of the parties concerned in Japan for rare disease patients. She says, "In various phases from incorporating to obtaining the designation as an orphan drug, drug approval and drug pricing, we received support of many parties concerned, including the Pharmaceuticals and Medical Devices Agency (PMDA), the Ministry of Health, Labour and Welfare (MHLW), and JETRO. We faced various challenges, but those people around us worked as tirelessly as we did. As a result of everyone's efforts for rare disease patients, we are now able to sell *Juxtapid*. We are truly fortunate to have a great number of supporters in this regard."

Future outlook

Nine members of Aegerion—including Ms. Nakamura and three key officials responsible for Marketing Supervisor General, Quality Assurance and Safety Management—are currently working from the office in the Ark Mori Building, where JETRO also has its head office. Ms. Nakamura is enthusiastic about raising public awareness of the disease, saying, "For the first two years, we are intending to focus on disease awareness and medical education initiatives. Early diagnosis & treatment is key, especially for rare disease patients, hence, awareness initiatives are important to ensure appropriate treatment for each patient."

Support from JETRO

JETRO provided Aegerion with the information related to pharmaceutical jurisprudence and the systems for intractable and rare diseases, including the consulting service by industry advisors specializing in the medical area. JETRO also provided a free-of-charge temporary office. Ms. Nakamura says, "JETRO was my First Stop in Japan and an excellent initial resource. I often referred to JETRO's booklet "Laws & Regulations on Setting up Business in Japan" on topics related to Corporate Law, Employment Law, Tax and Finance as I was setting up my business in Tokyo. JETRO is a reliable, resourceful organization. I highly recommend "startup" businesses or companies that are considering establishing business in Japan to reach out to JETRO for advice and consultation."

In front of the office with Ms.Nakamura & JETRO staff.

(Interviewed in January 2017)

Corporate history

2005 Aegerion Pharmaceuticals Inc. established in the U.S.
2012 Lomitapide approved by the FDA for HoFH
2013 The Japanese subsidiary established in Tokyo
Lomitapide approved by the EMA
Lomitapide designated as an orphan drug for HoFH in Japan (September)
2014 The Japanese Phase III clinical study began
2016 Japanese NDA (New Drug Application) was submitted on January 2016
Lomitapide approved (September), *Juxtapid* released on the market (December)

AEGERION PHARMACEUTICALS K.K.

Establishment:	2013
Business overview:	Development and sales of rare disease therapies
Parent company:	Aegerion Pharmaceuticals
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URL:	http://www.aegerion.co.jp/

JETRO's support

—Consultation on company registration, tax and labor laws.
—Consultation by Industrial Advisor（Biotechnology / Life Science）
—Provision of temporary office
—Provision of information on grants
—Provision of information on obtaining the Marketing Approval Holder (MAH)