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Otsuka and R-Pharm Announce Licensing Agreement to Commercialize Deltyba™ (Delamanid) for Multidrug-Resistant Tuberculosis (MDR-TB) in Russia and CIS Countries

Otsuka Pharmaceutical Co. Ltd. (Otsuka) and leading Russian pharmaceutical company R-Pharm JSC (R-Pharm), have entered into a licensing agreement to manufacture and commercialize Deltyba™ (delamanid) for the treatment of adults with pulmonary multidrug-resistant tuberculosis (MDR-TB) in the Russian Federation and the Commonwealth of Independent States (CIS).

Delamanid was discovered and developed by Otsuka and is currently marketed by the company under the brand name Deltyba™. Under the terms of the agreement, Otsuka's subsidiary, Otsuka Novel Products GmbH (ONPG) has granted R-Pharm a non-transferable license to register Deltyba™ in the Russian Federation and commercialize the product following regulatory approval. Both parties have also entered into discussions to develop a technology transfer plan to facilitate local manufacturing of Deltyba™. Following the successful submission of a regulatory dossier in the Russian Federation, R-Pharm may expand registration and commercialization activities in additional CIS countries.

The Russian Federation has one of the highest TB burdens in the world. In 2015 more than 15,000 Russian citizens died from TB and, along with India and China, accounted for nearly half of global MDR/Rifampicin resistant-TB cases that year.[1] At the same time, the Russian Federation is also playing a leading role in bringing together international organizations, national governments, tuberculosis experts and other stakeholders to address the global TB crisis. The country will play host to the first WHO Global Ministerial Conference, November 16 and 17 in Moscow.

"Japan and Russia share a long history of economic cooperation. By signing this agreement, Otsuka and R-Pharm continue that tradition while bringing a new treatment option to patients suffering from this deadly form of TB," said Tatsuo Higuchi, president and representative director. "Thanks to this important collaboration between our two companies, Otsuka continues expanding access to Deltyba in high-burden MDR-TB countries around the world."

"Recently, although we are seeing a decrease in the number of tuberculosis patients in Russia, we are increasingly confronted with cases where the disease becomes resistant to the types of therapy used", said Vasily Ignatiev, chief executive officer of R-Pharm. "Cooperation with Otsuka will help to increase the availability of effective drugs intended for the treatment of multidrug-resistant tuberculosis in Russia. It will help provide thousands of Russians stricken with the disease that are resistant to classical therapies a chance for a healthier life."

Deltyba™ is registered in the European Union, Japan, the Republic of Korea, Hong Kong and Turkey. Additional filings are pending in China, India, Indonesia, Peru, the Philippines, and South

Africa. To date, more than 3,000 treatment courses of Deltyba™ have been distributed in over 50 countries.

About Deltyba™

The efficacy of Deltyba™ was studied in a large, randomised, placebo-controlled phase 2 trial that included a 2-month treatment period and a 1-month follow-up of 481 MDR-TB patients (Trial 204), with 213 patients continuing to a 6-month open-label treatment trial (Trial 208), and concluding with a 24-month follow-up study of 421 out of the originally randomized 481 patients (Trial 116). Adding 100 mg Deltyba™ twice daily to a WHO-recommended OBR was associated with a statistically significant 53% increase (p=0.008) in the percentage of patients achieving SCC at 2 months (64/141, 45.4%) compared to those with placebo added (37/125, 29.6%).[2] The reported mortality rate was lower in patients receiving Deltyba™ for at least 6 months compared with those receiving Deltyba™ for 2 months or no Deltyba™ (2/192 (1.0%) v 19/229 (8.3%); p<0.001).[3]

Clinical trial results demonstrated that Deltyba™ is well tolerated with adverse events evenly distributed in the Deltyba™ and placebo treatment groups with the exception of QT prolongation. Electrocardiogram QT prolongation was reported in 9.9% (16/161) of patients receiving Deltyba™ as 100 mg twice daily compared to 3.8% (6/160) of patients receiving placebo plus OBR. This was not accompanied by any clinical symptoms such as syncope or arrhythmias.[2]

Publication of results of the phase 3 study to confirm the safety and efficacy of Deltyba™ is expected in 2018, and a paediatric investigational programme is underway.

About TB & MDR-TB

Tuberculosis (TB), an airborne infectious disease, is among the top causes of death in the world and is the leading infectious disease killer. Drug resistance poses a real challenge to fighting and treating TB. Globally in 2015, nearly half a million people developed MDR-TB, an infection resistant to at least isoniazid and rifampicin, the two most commonly used first-line TB drugs.[1] Mycobacterial MDR strains with additional resistance to at least one fluoroquinolone drug and a second-line injectable agent are defined as extensively drug-resistant (XDR). Secondary or acquired resistance has its roots in inappropriate treatment.

Resistance to anti-tuberculosis drugs worsens the prognosis for a successful treatment outcome. The treatment of MDR-TB combines at least four drugs – active or presumed active against the resistant strain – for an extended period of up to 20 months of more depending on patient response. The anti-TB drug combinations are chosen depending on the patterns of resistance from drug susceptibility testing and tolerance.

TB is the leading killer of HIV-positive people: about 35% of HIV deaths were due to TB in 2015. That year, there were an estimated 1.2 million new cases of TB amongst people who were HIV-positive, including 11,000 in the Russian Federation.[1]

About R-Pharm

R-Pharm is a Russian private pharmaceutical company founded in 2001, which employs over 3,500 highly qualified specialists in over 60 branches. Turnover reached over RUR 74,5 billion + in 2016. R-Pharm operates in Russia and CIS, USA, Germany, Japan, Turkey/MENA and India. The company is involved in R&D, manufacturing, marketing, sales and distribution of innovative pharmaceutical products from a broad number of therapeutic areas in specialty/hospital care. The company has operational GMP compliant manufacturing sites at Yaroslavl, Kostroma and Novosibirsk (Russia) and Illertissen (Germany). R-Pharm is building a modern Pharmoslavl facility for the synthesis of active pharmaceutical ingredients in Rostov (Russia).

About Otsuka

Otsuka Novel Products GmbH (ONPG), based in Munich, Germany, is dedicated to finding innovative solutions to fight the global pandemic of tuberculosis (TB). As the European marketing authorization holder for Deltyba™, Otsuka Novel Products GmbH works in collaboration with other Otsuka Group companies, partners, non-governmental organisations and other stakeholders, to expand global access to Deltyba™ and fight multidrug-resistant TB.

ONPG is a part of Otsuka Pharmaceutical Company, Ltd., a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan. Otsuka Pharmaceutical is a global healthcare company with the corporate philosophy: “Otsuka - people creating new products for better health worldwide.” Otsuka researches, develops, manufactures and markets innovative products, with a focus on pharmaceutical products to meet unmet medical needs and nutraceutical products for the maintenance of everyday health.

References:

[1] World Health Organization. Global tuberculosis report 2016. WHO/HTM/TB/2016.13.

[2] Gler MT, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *New England Journal of Medicine* 2012; **366**: 2151–2160.

[3] Skripconoka V, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *European Respiratory Journal* 2013; **41**: 1393–1400.