



Servier Receives Positive CHMP Opinion for LONSURF® (trifluridine/tipiracil) for Refractory Metastatic Colorectal Cancer

Recommendation is based on the RECOURSE study results demonstrating survival advantage for patients with refractory disease

Suresnes (France), 26 February 2016 – Servier today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion, recommending LONSURF® (trifluridine/tipiracil), formerly known as TAS-102, for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

“The positive CHMP opinion for LONSURF marks our entry into the field of solid tumors, but more importantly, it is an important step forward in the treatment of patients with metastatic colorectal cancer,” said Patrick Therasse MD, PhD, Director & Head of Development, Oncology at Servier. “Patients with mCRC who do not respond to standard therapies currently have limited therapeutic options. The availability of an oral treatment that could help to extend overall survival will be an important advantage for patients.”

The CHMP positive opinion is based on data from the international, double-blind, placebo-controlled Phase III RECOURSE study, which investigated the efficacy and safety of LONSURF with best supportive care (BSC) compared to placebo with BSC in 800 patients with previously treated mCRC. The trial met the primary endpoint of statistically significant improvement in overall survival (OS). Results demonstrated a 32% reduction in risk of death compared to BSC (HR=0.68; 95% CI: 0.58 to 0.81 p<0.001) and an improvement of 1.8 months of median OS (median OS was 7.1 for LONSURF vs 5.3 months for placebo). The most frequently observed side effects (≥ 30%) in patients receiving LONSURF were neutropenia, nausea, fatigue, anemia and leucopenia.^{1,2}

An updated OS analysis in 89% of events, this year presented at ASCO GI, confirmed the clinically meaningful and statistically significant survival benefit of LONSURF with BSC compared to placebo with BSC. This translates into a 31% relative reduction in the risk of death and an improvement of 2 months in the median OS. The median OS was 7.2 months for LONSURF with BSC vs 5.2 months for placebo with BSC (HR=0.69; 95% CI: 0.59 to 0.81; p<0.0001), this translated into 1-year survival rates of 27.1% and 16.6%, respectively.^{2,3}

The CHMP positive opinion will now be reviewed by the European Commission and if marketing authorization is granted, LONSURF will be approved in the 28 member countries of the European Union (EU), as well as Iceland, Lichtenstein and Norway.

In June 2015, Servier entered into an exclusive license agreement with Taiho Pharmaceutical Co., Ltd. for the co-development and commercialization of LONSURF. Under the terms of the agreement, Servier will commercialize LONSURF in Europe and other countries outside of the United States, Canada, Mexico and Asia. Taiho Pharmaceutical retains the right to develop and commercialize LONSURF in the United States, Canada, Mexico, and Asia and to manufacture and supply the product.



About Metastatic Colorectal Cancer

There remains a high unmet need in the treatment of colorectal cancer (CRC), which was the second leading cause of cancer-related deaths in Europe in 2012, responsible for 215,000 deaths.⁴

Approximately 25% of patients with CRC present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases.⁵ This contributes to the high mortality rates reported for CRC; the 5-year survival rate of patients diagnosed with stage IV mCRC is about 11%.⁶

About LONSURF

LONSURF is currently available in Japan for the treatment of unresectable advanced or recurrent CRC and in the United States for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine -, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.^{7,8} LONSURF is an oral combination anticancer drug of trifluridine (FTD) and tipiracil (TPI), whose primary mechanism of action differs from fluoropyrimidines. FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

About Servier

Servier is an independent research-based pharmaceutical company headquartered in France. With a strong international presence in 148 countries and 92% of its medicines being prescribed outside of France, Servier employs more than 21,200 people worldwide. In 2015, the company recorded a turnover of 3.9 billion euros of which 24% was reinvested in research and development. Currently, there are nine new molecular entities in clinical development for oncology respectively in breast, lung and other solids tumors as well as various leukemias and lymphomas.

This portfolio of innovative cancer treatments is being developed with various partners worldwide, and covers different hallmarks of cancer including cytotoxics, proapoptotic, targeted, immune and cellular therapies.

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¹ Mayer RJ, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. *N Engl J Med* 2015; 372:1909-19.

² LONSURF Summary of Product Characteristics

³ TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: Final survival results of the phase III RECURSE trial. *J Clin Oncol* 34, 2016 (suppl 4S; abstr 634) Available at: <http://meetinglibrary.asco.org/content/159397-173> Accessed February 2016

⁴ Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49: 1374–1403.

⁵ Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2014) 25 (suppl 3): iii1-iii9.

⁶ American Cancer Society. Colorectal Cancer. Available at:

<http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-survival-rates> Accessed February 2016

⁷ FDA News Release. FDA approves new oral medication to treat patients with advanced colorectal cancer. 22 September 2015. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm463650.htm> Accessed February 2016



⁸ Taiho Pharma. Taiho's Lonsurf® (trifluridine and tipiracil hydrochloride) Tablets Approved in Japan for Treatment in Advanced Metastatic Colorectal Cancer. Available at: <http://www.taiho.co.jp/english/news/20140324.html> Accessed February 2016