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Pierre Fabre Laboratories receives European Commission Approval for BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a *BRAF^{V600E}* mutation

- *European approval is based on results from the Phase II PHAROS trial, which showed a meaningful clinical benefit to BRAF^{V600E} mutated advanced NSCLC patients with an objective response rate (ORR) of 75% in treatment-naïve patients and 46% in previously treated patients.[1-3] The safety profile is consistent with that observed in the approved metastatic melanoma indication.[1]*
- *The approval follows a positive opinion issued on July 25 by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)*

Castres, France, August 30, 2024 – Pierre Fabre Laboratories announced today that the European Commission (EC) has approved BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a *BRAF^{V600E}* mutation. The approval is based on the results from the Phase II PHAROS trial, a global, open-label, multicentre, non-randomised trial to determine the efficacy and safety of BRAFTOVI® + MEKTOVI® in treatment-naïve and previously treated patients with *BRAF^{V600E}* mutant metastatic NSCLC.[1]

"We are pleased to be able to extend the treatment of BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib) to adult patients with advanced NSCLC with a *BRAF^{V600E}* mutation in Europe" said Eric Ducournau, Chief Executive Officer of Pierre Fabre Laboratories. "There are currently limited targeted treatment options for *BRAF^{V600E}* mutant NSCLC patients, so this approval is a significant milestone as BRAFTOVI® + MEKTOVI® will give patients the option of an additional effective targeted therapy."

The EC decision, following a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) issued on 25 July, is based on the results from the Phase II PHAROS trial.[1-3] At primary analysis (cut-off date: September 22, 2022), the primary endpoint of the trial (objective response rate [ORR] determined by independent radiology review [IRR]) was met. In the treatment-naïve population (n=59), the ORR was 75% (95% CI: 62, 85), including 15% complete responses (CRs) and 59% partial responses (PRs).[1-3] Updated results with an additional 10-month follow-up showed that 64% of patients maintained a response for at least 12 months, with a median duration of response (mDOR) per IRR of 40 months (95% CI: 23.1, not estimable [NE]).[2,3]*

For those patients who had received prior therapy (n=39), the ORR by IRR was 46% (95% CI: 30, 63), including 10% CRs and 36% PRs at primary analysis.[1] Updated results with an additional 10-month follow-

up showed that 44% of patients maintained a response for at least 12 months with a mDOR of 16.7 months (95% CI: 7.4, NE).[2,3]*

The most common treatment-related adverse events (TRAEs ≥20%) were nausea (50%), diarrhoea (43%), fatigue (32%), and vomiting (29%). Treatment-related serious AEs occurred in 14% of patients, with the most common being colitis (3%). One grade 5 TRAE of intracranial haemorrhage was reported.[1]

"The EC approval highlights our ongoing commitment to bring meaningful change to patients with diseases such as lung cancer where there is a high unmet need" said Núria Perez-Cullell, Head of Medical, Patient, and Consumer Affairs, Pierre Fabre Laboratories. **"Through our longstanding partnership with Pfizer, we have been able to utilize our capabilities and experience to deliver this innovative treatment combination for patients with BRAF^{V600E} mutant advanced NSCLC. We remain committed to harnessing the full potential of our clinical development programme so that we can continue to bring promising targeted oncology compounds to patients in Europe."**

On 12th October 2023, Pierre Fabre's partner Pfizer announced the approval of BRAFTOVI® + MEKTOVI® by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with *BRAF^{V600E}* mutant metastatic NSCLC, as detected by an FDA approved test.[4] BRAFTOVI® + MEKTOVI® are currently approved in Europe and other countries for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF^{V600}* mutation.[5,6] BRAFTOVI® , in combination with cetuximab, is also approved in Europe and other countries for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a *BRAF^{V600E}* mutation who have received prior systemic therapy.[5]

**Results for mDOR from a sensitivity analysis considering new anti-cancer therapy as an event in addition to progression and death are 23.1 months in treatment-naïve patients (14.8, NE) and 12.0 months (6.3, NE) in previously treated patients.[2]*

About PHAROS

PHAROS (NCT03915951) is an on-going open-label, single arm, multicentre, non-randomised Phase II trial to determine the efficacy and safety of BRAFTOVI® (encorafenib 450 mg QD) in combination with MEKTOVI® (binimetinib 45 mg BID) in 98 patients with advanced NSCLC with a *BRAF^{V600E}* mutation who are either treatment-naive or who have been previously treated with platinum-based chemotherapy and/or anti-PD-1/PD-L1 inhibitor therapy. Mutations were identified using next-generation sequencing or polymerase chain reaction tests performed at the patient's local laboratory. The primary endpoint is confirmed ORR per RECIST v1.1, by independent radiology review (IRR); secondary objectives comprise additional efficacy endpoints including duration of response (DOR), PFS, and OS as well as safety. The trial is being conducted across 56 sites in: Italy, the Netherlands, South Korea, Spain, and the U.S.

The PHAROS trial is sponsored by Pfizer Inc. and conducted with support from Pierre Fabre Laboratories.

About *BRAF^{V600E}* mutant advanced Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of cancer-related deaths, with over 1.8 million deaths worldwide annually.[7] Globally, lung cancers make up 12.4% of all cancers with over 2.4 million new cases every year. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 80% of all lung cancers.[8,9]

Currently, it is estimated that up to 69% of advanced NSCLC patients have druggable mutations in numerous genes.[10]

BRAF^{V600E} mutations occur in approximately 1-2% of NSCLC cases.[11] It stimulates tumour cell growth and proliferation by altering the MAP kinase (MAPK) signalling pathway. Inhibition of both *BRAF* and the downstream mitogen activated protein kinase (*MEK*) pathway has been shown to improve response rates in patients compared with BRAF inhibition alone.[1,12]

Precision has made great progress in the treatment of lung cancer for NSCLC patients with genetic alterations, such as *BRAF*^{V600E} mutations, that can be detected using biomarker tests.[13,14] Advances in targeted therapy and more widespread use of biomarker testing have been associated with significant improvements in population-level NSCLC mortality in recent years.[15]

About BRAFTOVI® + MEKTOVI®

BRAFTOVI® (encorafenib), a potent and highly selective BRAF inhibitor with a distinct pharmacological profile compared with other BRAF inhibitors, and MEKTOVI® (binimetinib), a potent and selective MEK inhibitor, inhibit kinases in the MAPK pathway – which is constitutively activated in *BRAF*^{V600E} mutant NSCLC - resulting in clinically relevant anti-tumour activity. Uncontrolled activation of this pathway has been shown to occur in many cancers, including melanoma, CRC, and NSCLC.[1,16]

In 2018, the European Commission (EC) approved BRAFTOVI® + MEKTOVI® for adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation. The approval was based on results from the randomised, active-controlled, open-label, multicentre Phase III COLUMBUS trial.

In 2020, the EC approved BRAFTOVI® in combination with cetuximab, for the treatment of adults with metastatic CRC with a *BRAF*^{V600E} mutation who have received prior systemic therapy. The approval was based on results from the randomised, active-controlled, open-label, multicentre Phase III BEACON CRC trial.

Pfizer has exclusive rights to commercialise BRAFTOVI® and MEKTOVI® in the U.S., Canada, and all countries in the Latin American, African, and Middle Eastern regions; Ono Pharmaceutical Co., Ltd. has exclusive rights to commercialise both products in Japan and South Korea; Medison has exclusive rights in Israel; and Pierre Fabre Laboratories has exclusive rights in all other countries, including Europe and Asia-Pacific.

The full product and safety information for the use of BRAFTOVI® and MEKTOVI® are outlined in the Summary of Product Characteristics (SmPC), published in the European public assessment report (EPAR) and available in all official EU languages. The full SmPCs can be accessed at: https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf and https://www.ema.europa.eu/en/documents/product-information/mektovi-epar-product-information_en.pdf

About Pierre Fabre Laboratories

Pierre Fabre Laboratories is one of Europe's leading pharmaceutical companies. For over 40 years, it has established itself as an international player in oncology, mastering the entire value chain from R&D to marketing. Its portfolio of oncology specialties covers colorectal, breast, lung and skin cancers, as well as certain hematologic malignancies and precancerous dermatological conditions such as actinic keratosis. In 2023, its oncology revenue amounted to nearly 500 million euros, over 90% of which was generated outside France.

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In 2023, Pierre Fabre Laboratories posted 2.83 billion euros in revenue, 70% of which came from international sales in 120 countries. Its portfolio includes several international brands and medical franchises such as Pierre Fabre Innovative Oncology, Pierre Fabre Medical Dermatology, Pierre Fabre Pharmaceutical Care, Eau Thermale Avène, Ducray, A-Derma, Klorane, René Furterer and Même Cosmetics.

Historically based in the southwest of France and manufacturing 95% of its products in France, Pierre Fabre Laboratories employs over 10,000 people worldwide. Its annual R&D budget amounts to nearly 200 million euros, of which about 50% is dedicated to targeted therapies in oncology and 40% to skin health and care solutions.

Pierre Fabre Laboratories' majority shareholder (86%) is the eponymous Foundation, which is recognized by the French government as being a public–interest foundation. This capital structure guarantees the company's independence and long-term vision. Dividends paid to the Pierre Fabre Foundation enable it to design and finance humanitarian healthcare-access programs in developing countries. Employees are the company's secondary shareholder, through an international employee shareholding plan.

Pierre Fabre Laboratories' sustainability policy has been assessed by the independent AFNOR Certification body and has been awarded the "Exemplary" level of its CSR label (ISO 26 000 standard for sustainable development).

For more information, visit www.pierre-fabre.com, @Pierre Fabre Oncology.

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