News Release

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European Commission Approves IMBRUVICA® (ibrutinib) in a Fixed-Duration Combination Regimen for Adult Patients with Previously Untreated Chronic Lymphocytic Leukaemia (CLL)

Approval marks the first all-oral, once-daily, fixed-duration Bruton's tyrosine kinase (BTK) inhibitor-based regimen for first-line treatment of CLL

BEERSE, BELGIUM, 4 August 2022 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the European Commission granted marketing authorisation for the expanded use of IMBRUVICA® (ibrutinib) in an all-oral, fixed-duration (FD) treatment combination with venetoclax (I+V) for adults with previously untreated chronic lymphocytic leukaemia (CLL). The approval is based on the pivotal Phase 3 GLOW study that demonstrated superior progression-free survival (PFS) in patients treated with I+V versus chlorambucil-obinutuzumab (Clb+O), and the FD cohort of the Phase 2 CAPTIVATE study, which showed deep and durable responses in patients treated with I+V, including those with high-risk features.[1,2]

"Developing innovative therapies remains vitally important in CLL, to ensure we have the option and ability to best tailor treatment to meet individual patient needs and preferences," said Edmond Chan, MBChB, M.D. (Res), EMEA Therapeutic Area Lead Haematology, Janssen-Cilag Limited. "Over the past 11 years, the efficacy and safety profile of ibrutinib has been established in clinical trials and real-world settings. With this approval, healthcare professionals will now have the flexibility to use ibrutinib either in a fixed-duration combination with venetoclax or as a continuous monotherapy in first-line CLL."

In Europe, ibrutinib is already approved as a continuous therapy in several indications across three blood cancers (CLL, mantle cell lymphoma and Waldenström's macroglobulinaemia).[3] In CLL, patient outcomes have improved over the last decade.[4] A wave of innovation, including the advent of novel oral therapies that target the underlying disease biology, has shifted the standard of care from chemoimmunotherapy to targeted agents and combination therapies.[4] Unmet needs remain, including time-limited combinations of targeted therapies that provide durable remissions and the flexibility to better tailor first-line therapy.**Error! Bookmark not defined.**

"The distinct and complementary mechanisms of action of ibrutinib and venetoclax, and the potential of this combination regimen to provide treatment-free remissions, mark important progress for how we approach first-line CLL therapy," said Arnon Kater[†], M.D., Ph.D., Deputy Head of Haematology, Amsterdam University Medical Centres, University of Amsterdam and Chairman of the HOVON CLL Working Group, the Netherlands and GLOW principal study investigator. "These highly active blood cancer treatments not only combine to deliver superior progression-free survival versus chlorambucil plus obinutuzumab, but also demonstrate robust disease clearance in lymphoid tissue, blood and bone marrow, and early sustainability of those responses after stopping treatment."

The EC approval is supported by data from the pivotal Phase 3 GLOW study (NCT03462719), which demonstrated that I+V was superior to Clb+O with respect to the primary endpoint, PFS assessed by an independent review committee, in elderly or unfit patients with CLL (PFS hazard ratio [HR]: 0.216; 95 percent confidence interval [CI], 0.131 to 0.357; P<0.001).**Error! Bookmark not defined.** The improvement in PFS with I+V was consistent across predefined subgroups, including older patients and those with comorbidities and high-risk features.[1] It is also supported by the FD cohort of the Phase 2 CAPTIVATE study (NCT02910583) which evaluated I+V in patients with previously untreated CLL who were 70 years or younger, including patients with high-risk CLL disease.**Error! Bookmark not defined.**

Data from these studies were recently published in *NEJM Evidence***Error! Bookmark not defined.** and *Blood,***Error! Bookmark not defined.** respectively, and primary analyses were originally featured as oral presentations at the European Hematology Association (EHA) 2021 Congress. Secondary analyses from GLOW were presented at the American Society of Hematology (ASH) 2021 Annual Meeting, and additional data from the CAPTIVATE study including clinical outcomes at three years and evidence of immune restoration post-treatment were presented at the EHA 2022 Congress.

Updated data for both studies showed the safety profile of the I+V regimen was consistent with known safety profiles of ibrutinib and venetoclax.[1,2] In GLOW, the most common adverse events (AEs) were diarrhoea (50.9 percent) and neutropenia (41.5 percent) in the I+V arm and neutropenia (58.1 percent) and infusion-related reactions (29.5 percent) in the Clb+O arm.**Error! Bookmark not defined.** AEs of Grade 3 or greater occurred in 75.5 percent and 69.5 percent of patients in the I+V and Clb+O arms, respectively.**Error! Bookmark not defined.** Any-grade atrial fibrillation occurred in 15 patients (14.2 percent) receiving I+V and two patients (1.9 percent) receiving Clb+O, however, only two patients (1.9 percent) discontinued ibrutinib due to atrial fibrillation while continuing venetoclax.[1] Although overall survival data is not mature, with a median follow-up of 34 months, there were 11 deaths in the I+V arm and 16 deaths in the Clb+O arm (HR: 0.760; 95 percent CI, 0.352 to 1.642).[1] In the CAPTIVATE FD cohort, the most common AEs were diarrhoea (62 percent), nausea (43 percent), neutropenia (42 percent), and arthralgia (33 percent) and were primarily Grade 1 or 2 in severity.**Error! Bookmark not defined.** The most common Grade 3/4 AEs were neutropenia (33 percent), hypertension (6 percent), and neutrophil count decreased (5 percent). Serious AEs occurred in 36 patients (23 percent) and one fatal AE occured.**Error! Bookmark not defined.**

"Ibrutinib is the first approved BTK inhibitor globally, which has helped transform outcomes and quality of life for patients living with blood cancers, such as CLL," said Craig Tendler, M.D., Global Head of Late Development, Diagnostics & Medical Affairs, Hematology & Oncology, Janssen Research & Development, LLC. "This approval reinforces our relentless ambition to advance and optimise treatment regimens, including this all-oral, once-daily, fixed-duration combination of ibrutinib-venetoclax, delivering deep and durable remissions for patients with previously untreated CLL."

#ENDS#

About Ibrutinib

Ibrutinib is a once-daily oral medication that is jointly developed and commercialised by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.[3] Ibrutinib blocks the Bruton's tyrosine kinase (BTK) protein, which is needed by normal and abnormal B-cells, including specific cancer cells, to multiply and spread.[5] By blocking BTK, ibrutinib may help move abnormal B-cells out of their nourishing environments and inhibits their proliferation.[6]

Ibrutinib is approved in more than 100 countries and has been used to treat more than 250,000 patients worldwide.[7] There are more than 50 company-sponsored clinical trials,

including 18 Phase 3 studies, over 11 years evaluating the efficacy and safety of ibrutinib.[3,8] In October 2021, ibrutinib was added to the World Health Organization's Model Lists of Essential Medicines (EML), which refers to medicines that address global health priorities and which should be available and affordable for all.[9]

Ibrutinib was first approved by the European Commission (EC) in 2014, and approved indications to date include:[3]

- As a single agent or in combination with rituximab or obinutuzumab or venetoclax for the treatment of adult patients with previously untreated CLL
- As a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy
- As a single agent for the treatment of adult patients with relapsed or refractory (RR) mantle cell lymphoma (MCL)
- As a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. In combination with rituximab for the treatment of adult patients with WM

For a full list of adverse events and information on dosage and administration, contraindications and other precautions when using ibrutinib please refer to the Summary of Product Characteristics for further information.

About the GLOW study

The Phase 3 GLOW study (N=211; median age, 71 years) is a randomised, open-label trial which evaluated the efficacy and safety of first-line, fixed-duration I+V vs. Clb+O in elderly patients (≥65 years of age) with CLL/SLL, or patients aged 18-64 with a cumulative illness rating scale (CIRS) score of greater than six or creatinine clearance less than 70 mL/min, without del(17p) or known TP53 mutations.**Error! Bookmark not defined.** Patients in the study were randomized to receive either 3 cycles of ibrutinib lead-in, followed by 12 cycles of I+V (n=106), or 6 cycles of Clb+O (n=105).**Error! Bookmark not defined.** The primary end point was PFS assessed by an independent review committee.[1]

About the CAPTIVATE study

The Phase 2 CAPTIVATE study evaluated previously untreated adult patients with CLL who were 70 years or younger, including patients with high-risk disease, in two cohorts: an MRD-guided cohort (N=164; median age, 58 years) and a fixed-duration cohort (N=159; median

age, 60 years).[10] Patients in the fixed-duration cohort received 3 cycles of ibrutinib lead-in followed by 12 cycles of I+V (oral ibrutinib [420 mg/d]; oral venetoclax [5-week ramp-up to 400 mg/d]) and the primary endpoint was complete response (CR) rate.**Error! Bookmark not defined.**

About Chronic Lymphocytic Leukaemia

Chronic lymphocytic leukaemia (CLL) is typically a slow-growing blood cancer of the white blood cells.[11] The overall incidence of CLL in Europe is approximately 4.92 cases per 100,000 persons per year and is about 1.5 times more common in men than in women.[12] CLL is predominantly a disease of the elderly, with a median age of 72 years at diagnosis.[13]

While patient outcomes have dramatically improved in the last few decades, the disease is still characterised by consecutive episodes of disease progression and the need for therapy.[4] Patients are often prescribed multiple lines of therapy as they relapse or become resistant to treatments.[14]

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular, Metabolism & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com/EMEA. Follow us at www.twitter.com/janssenEMEA for our latest news. Janssen Pharmaceutica NV, Janssen Biotech, Inc., Janssen-Cilag Limited and Janssen Research & Development, LLC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

†Dr. Kater has served as a consultant to Janssen; he has not been paid for any media work.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding IMBRUVICA (ibrutinib). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, Janssen Pharmaceutica NV, Janssen-Cilag Limited, Janssen Biotech, Inc, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but

are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 2, 2022, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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