May 22, 2023

To our friends and colleagues in the mast cell disorder community,

Blueprint Medicines is excited to share that the U.S. Food and Drug Administration (FDA) has approved AYVAKIT® (avapritinib) for the treatment of adult patients with indolent systemic mastocytosis (ISM). AYVAKIT is not recommended for the treatment of ISM in people with low platelet counts (less than 50 X 10^9/L). AYVAKIT is the first and only therapy approved by the FDA for the treatment of ISM. It is a once-a-day tablet that targets the genetic mutation that is the underlying cause of ISM in about 95% of cases.

The road to this important milestone has been long and complex. The mast cell disorder community has worked tirelessly for decades to raise awareness and advocate for better care even before we were founded in 2011.

When we began to explore the possibility of research in systemic mastocytosis, two members of our small team attended a meeting organized by The Mast Cell Disease Society, where we met a woman living with ISM. She shared a powerful story about how the disease had impacted her life, including her debilitating and unpredictable symptoms that forced her to self-isolate and withdraw from her community. Hearing directly from someone living with ISM, along with our improved understanding of how challenging living with the disease can be, reinforced our commitment to research mast cell disorders.

At that time, no drug had ever been approved for ISM, and we knew we needed to pioneer a new path to achieve our goal. We traveled around the world to meet clinical experts who had deep knowledge of ISM and had developed ways to assess the course of disease and evaluate existing management approaches. Building on their work, we designed a new tool to assess ISM symptoms that could meet regulatory requirements and validated it with the help of people living with ISM who generously gave their time to participate in an observational study.

Then, Blueprint Medicines designed and initiated the PIONEER clinical trial of AYVAKIT, the largest therapeutic trial ever conducted in people with ISM, with about 50 clinical sites in more than a dozen countries. All clinical trials require tremendous effort, but the dedication and resilience of PIONEER trial participants, investigators and site staff were extraordinary. The COVID-19 pandemic required creative solutions to continue the study. The success of this trial, which underpins the FDA approval announced today, represents a remarkable step forward made possible by the decades of collaboration across the mast cell disorder community.

Our commitment does not end here. Blueprint Medicines is proud to continue our work alongside this community, to raise awareness of ISM, accelerate definitive diagnoses, generate data to better define the burden of the disease, collaborate with other stakeholders to educate and support patients throughout their journey, and more. We are also continuing our scientific research across other mast cell disorders beyond ISM, including chronic urticaria, with the goal of improving the lives of people living with these conditions.

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The entire Blueprint Medicines team wishes to express our sincere gratitude to the participants, families, investigators, and clinical site staff who have supported the PIONEER clinical trial. It is because of these critical contributions that we have been able to advance our research and bring this novel treatment to more people living with ISM. Our work would also not have been possible without the collaboration with patient advocacy organizations, including The Mast Cell Disease Society, who have helped further our understanding of the true burden of ISM.

No person with ISM should embark on this journey alone—and we at Blueprint Medicines will continue to join with advocates, clinicians, and others to stand by you, side by side.

Wishing you all the best,

Kate Haviland
Chief Executive Officer

Fatima Scipione
Vice President, Global Patient Affairs

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INDICATION

AYVAKIT® (avapritinib) is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM).

Limitations of Use: AYVAKIT is not recommended for the treatment of patients with ISM with platelet counts of less than 50 x 10^9/L.

IMPORTANT SAFETY INFORMATION

AYVAKIT® (avapritinib) may cause serious side effects, including:

Intracranial Hemorrhage—Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (eg, subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT in clinical trials. In Advanced SM patients who received AYVAKIT at 200 mg daily, ICH occurred in 2 of 75 patients (2.7%) who had platelet counts ≥50 x 10^9/L prior to initiation of therapy and in 3 of 80 patients (3.8%) regardless of platelet counts. In ISM patients, no events of ICH occurred in the 246 patients who received any dose of AYVAKIT in the PIONEER study.

Monitor patients closely for risk factors of ICH which may include history of vascular aneurysm, ICH or cerebrovascular accident within the prior year, concomitant use of anticoagulant drugs, or thrombocytopenia.

Symptoms of ICH may include headache, nausea, vomiting, vision changes, or altered mental status. Advise patients to seek immediate medical attention for signs or symptoms of ICH.

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Permanently discontinue AYVAKIT if ICH of any grade occurs. In Advanced SM patients, a platelet count must be performed prior to initiating therapy. AYVAKIT is not recommended in Advanced SM patients with platelet counts <50 x 10^9/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks. After 8 weeks of treatment, monitor platelet counts every 2 weeks or as clinically indicated based on platelet counts. Manage platelet counts of <50 x 10^9/L by treatment interruption or dose reduction.

Cognitive Effects—Cognitive adverse reactions can occur in patients receiving AYVAKIT and occurred in 33% of 995 patients overall in patients who received AYVAKIT in clinical trials including: 28% of 148 Advanced SM patients (3% were Grade ≥3), and 7.8% of patients with ISM who received AYVAKIT + best supportive care (BSC) versus 7.0% of patients who received placebo + BSC (<1% were Grade 3). Depending on the severity and indication, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

Photosensitivity—AYVAKIT may cause photosensitivity reactions. In all patients treated with AYVAKIT in clinical trials (n=1049), photosensitivity reactions occurred in 2.5% of patients. Advise patients to limit direct ultraviolet exposure during treatment with AYVAKIT and for one week after discontinuation of treatment.

Embryo-Fetal Toxicity—AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use an effective method of contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks after the final dose.

Adverse Reactions—The most common adverse reactions (≥20%) in patients with Advanced SM were edema, diarrhea, nausea, and fatigue/asthenia.

The most common adverse reactions (≥10%) in patients with ISM were eye edema, dizziness, peripheral edema, and flushing.

Drug Interactions—Avoid coadministration of AYVAKIT with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided in patients with Advanced SM, reduce dose of AYVAKIT. Avoid coadministration of AYVAKIT with strong or moderate CYP3A inducers.

These are not all of the possible side effects of AYVAKIT. Call your doctor for medical advice about side effects. You are encouraged to report side effects to the FDA. Visit **FDA MedWatch** or call **1-800-FDA-1088**.

Please see the full Prescribing Information and Patient Information for AYVAKIT.

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