Pirtobrutinib Fact Sheet

Generic name: Pirtobrutinib (pronounced PIR toe BROO ti nib), formerly known as LOXO-305

Trade name(s): Jaypirca® (JAY-PIR-KAA) by Eli Lilly and Company

Drug type: Pirtobrutinib is an anti-cancer targeted therapy that is classified as a non-covalent Bruton tyrosine kinase (BTK) inhibitor. This drug works by blocking the protein called BTK that causes certain B cell cancers to grow and multiply, thereby helping to slow or stop the spread of the cancer cells.

Fast facts about pirtobrutinib

- **History:** Covalent BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib) have transformed the treatment of B cell cancers, including Waldenstrom's macroglobulinemia (WM). In China, the covalent BTK inhibitor orelabrutinib has been approved for the treatment of WM that has relapsed (disease has returned after treatment) or is refractory (disease has not responded to treatment). In Japan, the covalent BTK inhibitor tirabrutinib has gained approval for both front-line and relapsed/refractory WM treatment. Side effects may lead to their discontinuation, and the development of resistance to these drugs may limit their effectiveness. The Phase 1/2 BRUIN clinical trial evaluated pirtobrutinib, a highly selective non-covalent (reversible) BTK inhibitor, in patients with B cell cancers whose disease has relapsed or is refractory. Pirtobrutinib is the primary example of a non-covalent BTK inhibitor currently being investigated for treatment of WM, as well as for other B cell cancers.

- **Mechanism of action:** BTK protein signaling results in activation of pathways necessary for B cell functions. Unlike covalent BTK inhibitors, non-covalent inhibitors bind to the BTK protein without forming a permanent chemical bond, allowing it to hop on and off the BTK protein. Covalent BTK inhibitors bind to the BTK protein at a site called C481, but mutations in this site can cause the cancer cells to become resistant to these drugs. Non-covalent BTK inhibitors like pirtobrutinib do not bind to the C481 site; therefore, mutations in C481 do not develop, and this specific kind of resistance does not occur.

- **Potential benefit:** Non-covalent BTK inhibitors can target both the wild-type (unmutated) and mutated BTK protein; therefore, they may be effective in patients who have progressed on previous covalent BTK inhibitor therapies.

- **Dosage:** The usual dose is 200 mg given by mouth (orally) once daily, swallowed whole with water, with or without non-fatty food.

- **Clinical trials:** Currently, clinical trials in WM of non-covalent BTK inhibitors like pirtobrutinib are exploring their efficacy (in other words, how well they work) and their safety, particularly in those who were previously treated with covalent BTK inhibitors.

- **Side effects:** Studies of pirtobrutinib have linked its reduced cardiovascular and other side effects with its high selectivity (its ability to target the cancer cells while minimizing its impact on normal cells).

Beyond the fast facts about pirtobrutinib

What conditions are treated by pirtobrutinib?

Pirtobrutinib is approved by the US Food and Drug Administration (FDA) to treat adults with mantle cell lymphoma that has relapsed or is refractory and who have already received at least two treatments for their cancer, including a Bruton tyrosine kinase (BTK) inhibitor. This drug is also FDA-approved for adults with chronic lymphocytic leukemia or small cell lymphocytic lymphoma who have already received at least two treatments for their cancer, including a BTK inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor (such as venetoclax).

Without specific FDA approval for treating WM, pirtobrutinib prescribed for WM patients is given "off-label," signifying the drug is being used for an unapproved indication or in an unapproved age group, dosage, or route of administration. This ability to prescribe drugs for uses beyond officially approved indications is common in medicine and includes most other drugs used to treat WM, except for ibrutinib, zanubrutinib, and the combination of ibrutinib with rituximab. The National Comprehensive Cancer Network (NCCN) guidelines endorse pirtobrutinib to treat relapsed or refractory WM patients in certain circumstances. Country-specific expanded access programs are also available.

How does pirtobrutinib work?

Normal, healthy cells divide and grow in a precise, orderly way. Cancer cells, however, no longer have the normal mechanisms in place that control and limit cell division, resulting in rapid and uncontrollable growth.

All BTK inhibitors can interfere with a WM cancer cell's ability to grow or multiply. Covalent BTK inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, have been an important advancement in WM treatment. However, they do not cure the disease, and treatment and effectiveness can be limited by side effects and the cancer cells' ability to develop resistance to these drugs. In WM, approximately 50% of patients on covalent BTK inhibitors develop C481 mutations in BTK, leading to drug resistance and disease progression.

Pirtobrutinib is the leading member of a new generation of highly selective, non-covalent (reversible) BTK inhibitors that bind BTK distant from the C481 site. Although it too cannot cure WM, emerging data from clinical trials of pirtobrutinib show clear clinical activity in patients whose disease carries C481 mutations, as well as in patients without C481 mutations.

Studies have indicated that many patients who are intolerant to ibrutinib are able to tolerate acalabrutinib or zanubrutinib. Similarly, 94% of patients on pirtobrutinib who were intolerant to covalent BTK inhibitors (primarily ibrutinib) were able to tolerate pirtobrutinib. Pirtobrutinib could therefore potentially be used after discontinuation of ibrutinib because of toxicity, although the data for pirtobrutinib use after intolerance to acalabrutinib and zanubrutinib remain limited. The relative tolerability in head-to-head comparisons has not been determined in clinical trials for WM. Whether pirtobrutinib will be moved into earlier lines of therapy, including front-line therapy or prior to the use of covalent BTK inhibitors, remains an unanswered question. In the relapsed setting, combined agents are under active clinical development and assessment in clinical trials, including pirtobrutinib plus venetoclax in a Phase 2 trial.

Optimal treatment of patients who develop pirtobrutinib resistance is unknown. As available treatment options expand, personalizing therapy by selecting subsequent treatments based on predicted sensitivity becomes critical.

How is pirtobrutinib given?

Pirtobrutinib is available as a tablet in 50 mg and 100 mg doses, The recommended dosage for WM is 200 mg by mouth (orally) once daily, taken at the same time each day. Do not cut, crush, or chew the tablets. It is recommended that the tablet be swallowed whole with water, with or without food. If there is stomach upset, take pirtobrutinib with low fat food. High fat meals given with pirtobrutinib can affect the concentration of the drug in the bloodstream.

Side effects from the therapy may require treatment interruption, dosage reduction, or discontinuation. The dose may need to be reduced in patients with severe renal (kidney) impairment.

What are some of the benefits and risks of treatment with pirtobrutinib?

Since WM is currently not curable, the goal of pirtobrutinib therapy is to reduce the disease enough to provide symptom relief and reduce the risk of organ damage. In clinical trials, pirtobrutinib therapy has been generally well-tolerated and effective.

Pirtobrutinib has shown encouraging activity in patients with WM who were previously treated with a covalent BTK inhibitor, but the data are from an abstract (brief summary of findings) rather than a peer-reviewed manuscript (a full research paper that has been evaluated by experts in the field before being published in a scholarly journal). This means that the following data have not yet gone through a rigorous review process to ensure quality and accuracy. The multicenter Phase 1/2 BRUIN study of pirtobrutinib in patients with previously treated B cell cancers included 80 patients with WM, 63 of whom had previously received a covalent BTK inhibitor and 17 of whom had not. After treatment with pirtobrutinib, the major response rate (a fifty percent or greater reduction in IgM level) was 71.3% in all patients with WM. Breaking this down between

the two groups, the group previously treated with a covalent BTK inhibitor achieved a major response rate of 66.7%, while the group without previous BTK inhibitor therapy achieved a major response rate of 88.2%. The trial also reported the combined rate of complete responses (the complete absence of monoclonal IgM, abbreviated CR) and very good partial responses (a ninety percent or greater reduction in IgM level, abbreviated VGPR) for each group. The group previously treated with a covalent BTK inhibitor had a combined CR + VGPR of 23.8%, while the group without previous BTK inhibitor therapy achieved a combined CR + VGPR of 29.4%.

What are the side effects of pirtobrutinib?

The most common side effects of pirtobrutinib observed in the Phase 1/2 BRUIN trial of patients with B cell cancers included the following: fatigue (26%), diarrhea (22%), low counts of infection-fighting white blood cells called neutrophils (20%), and large areas of bruising caused by low numbers of blood-clotting cells called platelets (19%). Low rates of the typical side effects caused by covalent BTK inhibitors were observed: high blood pressure or hypertension (3%), bleeding or hemorrhage (2%), and a common type of irregular and rapid heartbeat called atrial fibrillation/flutter (1%). Overall, 2% of patients with WM discontinued the drug because of treatment-related side effects. The study's authors noted that, "one striking property of pirtobrutinib is the really low toxicity (number of side effects), especially for patients who experienced a lot of side effects with covalent BTK inhibitors."

Most people will not have all these side effects. If you experience any side effects, tell your healthcare provider. There are medications and strategies that can help lessen their severity.

How does pirtobrutinib compare to covalent Bruton tyrosine kinase inhibitors?

No direct comparisons have been made comparing outcomes of pirtobrutinib to covalent BTK inhibitors in WM. The data on pirtobrutinib as a treatment for WM are still evolving.

When should a healthcare provider be contacted right away?

Even though it is rare, some people may have serious side effects when taking pirtobrutinib. Inform your doctor right away if you have any of the following signs or symptoms, as you may need immediate medical attention:

- Allergic reactions—skin rash, itching, hives, swelling of the face, lips, tongue, or throat.
- Bleeding—bloody or black, tar-like stools, vomiting blood or brown material that looks like coffee grounds, red or dark brown urine, small red or purple spots on skin, unusual bruising or bleeding. Your risk of severe bleeding may increase if you are also taking blood thinner medicine.
- Heart rhythm changes—fast or irregular heartbeat, dizziness, feeling faint or lightheaded, chest pain, trouble breathing. Your risk for heart rhythm problems may be increased if you have high blood pressure or have had heart rhythm problems in the past.

- Infection—fever, chills, cough, sore throat, wounds that don't heal, pain or trouble when passing urine, general feeling of discomfort or being unwell
- Liver injury—right upper belly pain, loss of appetite, nausea, light-colored stool, dark yellow or brown urine, yellowing skin or eyes, unusual weakness or fatigue
- Low red blood cell level—unusual weakness or fatigue, dizziness, headache, trouble breathing

Side effects that usually do not require medical attention (report these to your care team if they continue or are bothersome):

- Bone, joint, or muscle pain
- Cough
- Diarrhea
- Fatigue

These are not all the side effects that can occur with pirtobrutinib. In general, it's always good practice to inform your healthcare provider if you experience any unusual symptoms. Some serious side effects may require changes in therapy, such as lowering the dose given, waiting longer between doses, or stopping the use of the drug. You may also report side effects to the FDA at 1-800-FDA-1088.

What are some self-care tips while taking pirtobrutinib?

The following are some things you need to do or know while taking this drug. Before starting treatment with pirtobrutinib, tell your doctor if you:

- Have any allergies to drugs, foods, or other substances (like latex for example).
- Have medical problems, especially kidney or liver disease.
- Are, or may be, pregnant. This drug can cause harm to an unborn baby. A pregnancy test will be done before you start pirtobrutinib to make sure you are not pregnant. You cannot breastfeed while taking this drug for one week after your last dose. Females who are able to become pregnant should use effective birth control (contraception) during treatment and for at least one week after the last dose of pirtobrutinib.
- Desire to father a child. Pirtobrutinib may impair fertility in some men; this may resolve after treatment, last several years, or be permanent. Discuss this with your doctor.
- Are taking medications that prevent or treat blood clots.
- Are taking any other medications or supplements. Some supplements (i.e. vitamin E) can increase the risk of bleeding. Pirtobrutinib may affect how other medications work, and other medications may affect the way this medication works. In particular, CYP3A inhibitors or inducers may interact with pirtobrutinib, and your doctor may need to change the dose of pirtobrutinib by increasing or reducing it or may suggest other changes to

your treatment plan to lower the risk of side effects and to make sure your medications work as intended.

While taking pirtobrutinib:

- Take this medication by mouth with water. Take it as directed on the prescription label at the same time every day. Do not cut, crush, or chew this medication. Swallow the tablets whole. You can take it with or without food. If it upsets your stomach, take it with food. Your healthcare team may change your dose or tell you stop taking this medication if you get side effects. Do not change your dose or stop taking it unless your healthcare team tells you to do so.
- If you think you have taken too much of this medicine, contact a poison control center or emergency room at once.
- If you miss a dose, take it as soon as you can unless it is more than 12 hours late. If it is more than 12 hours late, skip the missed dose. Take the next dose at the normal time.
- You may be at risk of infection so try to avoid crowds or people with infections, colds, or flu and wash your hands often.
- You may bleed more easily. Avoid contact sports or activities that could cause injury. Use an electric razor and a soft toothbrush to minimize bleeding.
- To help prevent/treat mouth sores, use a soft toothbrush and rinse three times a day with 1 teaspoon of baking soda mixed with 8 ounces of water.
- To reduce nausea, take anti-nausea medications as prescribed by your doctor and eat small, frequent meals. In general, drinking alcoholic beverages should be kept to a minimum or avoided completely.
- While taking pirtobrutinib, do not take aspirin or products containing aspirin unless your doctor specifically permits this.
- If you or your partner may get pregnant, use birth control while taking this drug and for one week after the last dose. Pirtobrutinib may cause harm to an unborn child.
- If you are going to need surgery or other procedure, tell your healthcare team that you are using this medication. You may need to discontinue this medication prior to the procedure.
- Tell your dentist and oral surgeon that you are taking this medication. You should not have major dental surgery while on this medication. See your dentist to have a dental exam and fix any dental problems before starting this medication. Take good care of your teeth while on this medication. Make sure you see your dentist for regular follow-up appointments.
- Keep pirtobrutinib out of the reach of children and pets.
- Store pirtobrutinib at room temperature, between 68-77 degrees F (20-25 degrees C); brief temperature excursions are permitted to 59-30 degrees F (15-30 degrees C). As with other medications, get rid of any unused medication after the expiration date.
- Do not share this medication with others, it is only for you.

How will I be monitored while taking pirtobrutinib?

You will be checked regularly by your doctor to monitor side effects and assess your response to therapy. Periodic blood work will be obtained to monitor your blood counts and evaluate the function of organs, such as your liver and kidneys.

Acknowledgments

The IWMF acknowledges the important contributions to treatment guidelines made by the National Comprehensive Cancer Network and the International Workshops on Waldenstrom Macroglobulinemia.

The IWMF also acknowledges Drs. Jorge Castillo and Shayna Sarosiek of Dana-Farber Cancer Institute for their medical review of this publication.

About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important vision, "a world without WM," and a mission to "support and educate everyone affected by Waldenstrom's macroglobulinemia (WM) to improve patient outcomes while advancing the search for a cure."

More information about Waldenstrom macroglobulinemia and the services and support offered by the IWMF, and its affiliate organizations, can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a business office at 6144 Clark Center Ave., Sarasota, FL 34238. The office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.