Bendamustine Fact Sheet

Generic name: bendamustine hydrochloride (pronounced ben-da-MUS-teen)

Trade name(s): Treanda®; Bendeka® by Teva; Belrapzo® by Eagle Pharmaceuticals

Drug type: Bendamustine is an anti-cancer chemotherapy drug that is classified as an "alkylating agent" because of the chemical way in which it damages DNA, resulting in cell death.

Fast facts about bendamustine

- Bendamustine is usually given in combination with rituximab (a combination called "Benda-R" or "BR") or sometimes with other drugs similar to rituximab which act in the same way. Typically, it is given in four to six monthly cycles. In people with very high IgM, doctors may choose to use bendamustine alone for the first one or two cycles to avoid a potentially dangerous surge in blood IgM that is sometimes caused by rituximab (IgM flare). The Benda-R combination is used for the rest of the cycles.
- The efficacy of Benda-R (in other words, how well it works) is about the same as the efficacy of ibrutinib or zanubrutinib, two other commonly used Waldenstrom's macroglobulinemia (WM) drugs.
- An advantage of Benda-R is that it is a "one-and-done" treatment, which does not require taking pills indefinitely. After the typical four- to six-month course of Benda-R treatments, no ongoing treatment is generally required, unless WM becomes active again (relapses) and requires further treatment. WM often doesn't relapse for many years after Benda-R treatment.
- In general, Benda-R is well-tolerated. However, in frail patients or people with many other medical issues, Benda-R may not be the best choice, although the typical dose or number of cycles may be reduced for frail patients.
- A side effect in some people is "cytopenia," which means the body doesn't make enough blood cells of one or more types, such as neutrophils (cells that fight bacterial infections), platelets (cells that form clots to stop bleeding), or red blood cells (which carry oxygen throughout the body). The cytopenia is typically short-lived, but can last a long time. This may result in infections, bleeding or bruising, and overall fatigue or shortness of breath.
- MYD88 and CXCR4 mutations do not typically affect how well a person responds to Benda-R. Some CXCR4 mutations do reduce the odds of responding well to BTK (Bruton tyrosine kinase) inhibitors.
- Another side effect is DNA damage. Bendamustine is designed to act by damaging the DNA of rapidly-dividing cells, but it can also damage DNA in normal cells. Although it is not common, this DNA damage can eventually lead to other forms of blood or bone marrow cancer in a small percentage of patients. For that reason, some doctors prefer not to use bendamustine in younger patients.
- Benda-R is given intravenously. Bendamustine may cause irritation of the veins and even permanent vein damage. Giving bendamustine in a highly diluted form helps

prevent vein damage. Another alternative is to have a port (or port-a-cath) (see below, "***How is bendamustine given?***") inserted before treatment is scheduled to begin.
- Patients who are actively receiving Benda-R are more susceptible to COVID and other infections and need to be especially cautious.
- Benda-R is less expensive than long-term ibrutinib or zanubrutinib use.

Beyond the fast facts about bendamustine

How is bendamustine used and what conditions are treated by bendamustine?

Bendamustine is a chemotherapy typically used in combination with rituximab (Rituxan®), and this combination is often referred to as "Benda-R" or "BR." Rituximab is a monoclonal antibody, so the combination of both drugs is sometimes called "chemoimmunotherapy" or CIT. Some doctors or insurance companies may prefer to use drugs similar to rituximab. This combination is a commonly used treatment for WM, a type of indolent B cell non-Hodgkin lymphoma (NHL). The combination is used in people being treated for the first time (first-line therapy), and, is also often used in people who were successfully treated previously but then the WM becomes active again (relapses).

Bendamustine is approved in many countries for the treatment of people with chronic lymphocytic leukemia (CLL) or indolent (slow-growing) B cell non-Hodgkin lymphomas that have progressed during or within six months of treatment with rituximab (Rituxan®) or a rituximab-containing regimen. Chemoimmunotherapy, such as Benda-R, is a common first-line therapy in Europe, North America, Asia-Pacific, and Latin America.

How does bendamustine 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 continued and uncontrolled cell growth.

All chemotherapy drugs interfere with a cancer cell's ability to grow or multiply. Many drugs attack cancer cells by interacting with the cell's genetic makeup (RNA or DNA) in such a way that they kill the cancer cell or prevent it from growing or dividing. Alkylating agents, like bendamustine, work by damaging the cells' DNA resulting in cell death.

How is bendamustine given?

Bendamustine is given as an intravenous (IV) infusion into a vein through a small needle in your arm and rituximab is administered either intravenously or subcutaneously (injected under the skin). There is no pill form of bendamustine. Your doctor will determine the appropriate dose and schedule (four vs. six cycles) of bendamustine based on several factors including your

height, weight, blood counts, age, and any specific medical issues you may have. Preferences about dose and cycles vary from country to country, as well as from doctor to doctor.

Intravenous injection of bendamustine often causes irritation to the veins and may result in permanent damage, even when all precautions are taken. Bendamustine may be administered at a doctor's office, the hospital, or an infusion center. Tell your nurse if you have any pain, burning, redness, swelling, or fluid leaking around the IV insertion site, as this drug may cause tissue damage if it leaks out of your vein into the surrounding skin. This is an important concern for WM patients who are administered Benda-R. Dilution of the IV infusion may reduce injury to the vein, or a port may be recommended. A port (otherwise known as a port-a-cath) is an intravenous (IV) line that is surgically implanted and resides completely under the skin. It consists of a one inch or two and one-half centimeters in diameter round piece of metal with a soft silicone top called the port and a catheter, which is the thin, flexible tube attached to the port. A port provides a more comfortable way for the patient to receive IV medications, such as chemotherapy. It can be removed when treatment is finished.

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

As for all WM treatments, the goal of Benda-R therapy for WM is symptom relief and reducing the risk of organ damage. Benda-R therapy is often effective, generally well-tolerated, of fixed duration, and relatively affordable compared to BTK inhibitors. It is useful for people with enlarged lymph nodes, livers, or spleens, or when a rapid response is needed. Another advantage is that it is used for a fixed duration of time (four or six cycles of treatment)—not as an ongoing, indefinite therapy.

Benda-R induces high and deep response rates (clinical benefits) in previously untreated WM, which translates into prolonged overall survival (how long a person lives after diagnosis, abbreviated OS) and progression-free survival (time from initiation of treatment to disease progression or death, abbreviated PFS). In a study of newly diagnosed patients with WM, this drug combination resulted in an overall response rate (the total percentage of patients who respond to a specific therapy, abbreviated ORR) of greater than 90% after six months of treatment with a median (midpoint of time) progression-free survival of 82 months (almost seven years). Even among those who relapsed, the median time to next treatment was 32 months.

MYD88 and CXCR4 mutations do not typically affect how well a patient responds to Benda-R. Some CXCR4 mutations reduce the odds of responding well to BTK inhibitors.

Patients need to be medically fit to tolerate this chemotherapy. Sometimes, a reduction in the bendamustine dose or in the number of cycles (from six to four, if there is a very good response) is recommended in frail and/or elderly patients without impact on progression-free survival.

Choice of therapy in relapsed WM should be individualized by taking previous treatments and patient characteristics into account, such as treatment duration, toxicity, age, other medical conditions (comorbidities) and MYD88 and CXCR4 mutational status. Bendamustine-based therapy is effective in previously treated (relapsed/refractory) WM because it produces high response rates and long lasting (durable) responses either as monotherapy or in combination with rituximab. Studies of patients with previously treated WM who received bendamustine-based therapy reported an overall response rate of 80-95%. Median progression-free survival in patients with previously treated WM was 13.2-58 months depending upon the study.

A disadvantage of bendamustine is that it is a DNA-damaging agent. It may cause mutations in the DNA of normal cells, which increases the risk of secondary cancer. In particular, occasional patients develop other bone marrow cancers such as acute myeloid leukemia (AML) or secondary myelodysplastic syndrome (MDS). For that reason, some doctors prefer not to use bendamustine in younger patients. Bruton tyrosine kinase inhibitors (BTKi's) or proteasome inhibitors are an important treatment option in young patients, in whom alkylator exposure with its long-term consequences pertaining to second hematologic malignancies may not be desirable.

Bendamustine is contraindicated in patients with a known allergy (hypersensitivity) to the drug or to the additive, polyethylene glycol 400, propylene glycol, or monothioglycerol. If one's IgM is greater than 4,000 mg/dL, rituximab should not be given due to risk of IgM flare (a surge in IgM levels). In those cases, bendamustine can be given alone for the first 1-2 cycles, with rituximab added at a later date. Approximately 10% of patients with WM will develop intolerance to rituximab, and ofatumumab can be substituted for rituximab.

What are the side effects of bendamustine?

Chemotherapy is most effective at killing dividing cells, which is why it is effective against WM cells. However, there are healthy cells in the body that are also affected by chemotherapy, such as those in the bone marrow (where new blood cells are made); as well as cells that line the mouth, stomach, and bowel and cells that grow hair. Damage to these healthy cells is what causes some of the common side effects of chemotherapy—resulting in low blood counts, mouth sores, nausea, diarrhea, and/or hair thinning, respectively. Fortunately, the normal cells will grow back, and most associated side effects will go away once treatment ends.

The most common side effects of bendamustine include the following: fatigue, fever, nausea and vomiting, diarrhea, constipation, loss of appetite, cough, headache, weight loss, difficulty breathing, rash, mouth irritation, low red blood cells (oxygen-carrying cells), low platelets (blood-clotting cells), and low white blood cells (infection-fighting cells).

Increased risk of infection is one of the most common side effects associated with Benda-R, especially cytomegalovirus, shingles, COVID, and bacterial pneumonia. *Pneumocystis jirovecii*

pneumonia (PJP) prophylaxis and the shingles vaccine can be considered for people receiving Benda-R. Long-term reduction (cytopenia) in the number of red and/or white blood cells and/or platelets can last a year or so in some people or may become permanent. This is a particular risk in older or more frail people with WM. Most people will not have all of 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 Benda-R compare to Bruton tyrosine kinase inhibitors (BTKi's)?

Both Benda-R and BTKi's are considered good treatment regimens (see table below). BR continues to play a central role in managing WM. Preferences vary from country to country (BTKi's are not available in all countries), as well as from doctor to doctor.

BTK Inhibitors (BTKi's) (Ibrutinib, Acalabrutinib, Zanubrutinib)	**Bendamustine/Rituximab (Benda-R)**
Taken by mouth as pills. Ibrutinib is typically taken once a day, acalabrutinib is taken twice a day, and zanubrutinib either once or twice a day.	Intravenous administration of Benda; rituximab is either intravenous or subcutaneous. Benda-R causes venous irritation, and in some cases, permanent vein damage.
Indefinite length of treatment. BTKi's have long progression-free survival (5+ years), similar to Benda-R.	Fixed duration, (usually 4-6 monthly cycles), with long progression-free survival (5+ years).
Response rate is >90% with BTKi's.	Benda-R has similar response rate of 90%.
Zanubrutinib has less severe toxicities with regard to cytopenias, so it may be better for older, more frail patients.	Reduction in dose and/or number of cycles may be necessary for older and frail patients. Toxicities, especially cytopenias, seen while in treatment, and long-term toxicities may occur.
Indefinite expense.	Benda-R is less expensive than long-term ibrutinib or zanubrutinib use.
Interferes with the growth and development of B cells, as long as the therapy is not stopped. May be better option for young patients.	Cancer cells are killed, and the marrow is cleaned out. Possible secondary malignancy can occur (AML, MDS).
BTKi's are less effective for wild-type (unmutated) MYD88 and some CXCR4 mutations, but zanubrutinib may provide better responses in these groups.	Generally, mutational status (CXCR4, MYD88) does not influence result.
BTKi's can cause cardiovascular adverse effects (i.e., atrial fibrillation/flutter and hypertension), although their incidence with zanubrutinib is less than with ibrutinib.	Benda-R is not particularly known for causing cardiovascular adverse effects.

When should a healthcare provider be contacted right away?

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

- Signs of an allergic reaction like a rash, itching, and hives; blistered or peeling skin; tightness in the chest or throat; trouble breathing, swallowing, or talking.
- Signs of infection like fever, chills, cough, and wounds that won't heal.
- Signs of bleeding like throwing up blood; blood in your urine; or black, red, or tarry stools.
- Signs of dehydration like dizziness; confusion; extreme fatigue, muscle pain or weakness; unable to pass urine; or a heartbeat that doesn't feel normal.
- Signs of liver problems like dark urine; light-colored stools; upset stomach, throwing up, or stomach pain; yellow skin or eyes.
- Signs of a rare but serious complication called tumor lysis syndrome, which occurs when large numbers of cancer cells are rapidly killed by the therapy. These cells release uric acid, potassium, and phosphorus into the bloodstream, which can lead to kidney failure. Tumor lysis syndrome usually occurs within 24-48 hours of therapy. Your doctor will prescribe fluids to keep you well-hydrated, and you may be given a drug called allopurinol that blocks uric acid production. Call your doctor right away if you have a fast or abnormal heartbeat; muscle weakness or cramps; trouble passing urine; upset stomach, vomiting, diarrhea; or feel extremely sluggish.

These are not all the side effects that can occur with bendamustine. 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.

What are some self-care tips while taking bendamustine?

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

- All other medicines you are taking, including prescription, over-the-counter (OTC), vitamins, and supplements. Do not take this medicine with clozapine. This medicine may also interact with the following medications: atazanavir, cimetidine, ciprofloxacin, enoxacin, fluvoxamine, medicines for seizures like carbamazepine and phenobarbital, mexiletine, rifampin, tacrine, thiabendazole, zileuton. This list may not include all possible interactions. Also tell your doctor if you smoke, drink alcohol, or use recreational drugs.

- **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 may cause harm to an unborn baby. If you could potentially become pregnant, a pregnancy test will be done before you start bendamustine to make sure you are not pregnant. You cannot breastfeed while taking this drug and for one week after your last dose.
  - Desire to father a child. Bendamustine may impair fertility in some men; this may resolve after treatment, last several years, or be permanent. Discuss this with your doctor.
  - Are considering cryopreserving eggs or sperm before the Benda-R. After treatment with Benda-R you may use cryopreserved eggs or sperm.
- **While taking bendamustine:**
  - Try to drink at least two to three quarts of fluid every 24 hours (particularly the 24 hours before and 48 hours following the infusion) unless you are instructed otherwise.
  - 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 bendamustine, do not take aspirin or products containing aspirin unless your doctor specifically permits this.
  - If you or your sex partner may get pregnant, use birth control while taking this drug and for some time after the last dose. Bendamustine may cause fetal harm. Ask your doctor how long to use birth control.

How will I be monitored while taking bendamustine?

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.

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About the IWMF

The IWMF, the only international organization dedicated to Waldenstrom's macroglobulinemia, is a patient-founded and patient-driven, nonprofit with a simple but compelling vision, "a world without WM," and a mission to "support and educate everyone affected by WM to improve patient outcomes while advancing the search for a cure."

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF, and its affiliate organizations, can be found on our website, iwmf.com. The office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.

The IWMF relies on donor contributions to fulfill its mission, and we welcome your support. You can contribute to the organization by visiting our website or by mailing a check to:

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Medical Disclaimer: The information presented here is intended for educational purposes only. It is not meant to be a substitute for professional medical advice. Patients should use the information provided in full consultation with, and under the care of a physician with experience in the treatment of WM. We discourage the use by a patient of any information contained herein without disclosure to his or her medical specialist.