

Fact Sheet

News from the IBD Help Center

Targeted Synthetic Small Molecules

Targeted synthetic small molecules are medications that help reduce inflammation by specifically targeting parts of the immune system that play a role in inflammation in the intestine and other organs. There are currently three FDA approved targeted synthetic small molecules to treat ulcerative colitis. There is currently one FDA approved targeted synthetic small molecules to treat adults with Crohn's disease.

JAK Inhibitors

JAK (Janus kinase) inhibitors are small molecules that are broken down in the gastrointestinal tract and directly absorbed into the bloodstream through the intestines. Due to their small size, they can be carried to nearly anywhere in the body through the bloodstream to work directly on the immune system. These small substances block multiple inflammatory pathways to help control IBD.

Tofacitinib (Xeljanz[®]) and upadacitinib (Rinvoq[®]) are JAK inhibitors that are FDA-approved to treat adult patients with moderate-to-severe ulcerative colitis. Upadacitinib (Rinvoq[®]) is also FDA-approved to treat adult patients with moderate-to-severe Crohn's disease. They are taken orally in pill form.

Common Side Effects:

- *Tofacitinib*: Upper respiratory tract infections (common cold, sinus infections), runny nose (nasopharyngitis), elevated cholesterol, headache, and anemia
- *Upadacitinib*: Headache, fatigue, acne, nausea, urinary tract infection, and elevated cholesterol

Risks/Safety:

- Taking tofacitinib or upadacitinib may include risk of serious infections, blood clots, certain types of cancer, and may increase risk of death or major cardiovascular events. Notably, these more serious events were seen in rheumatoid arthritis patients treated with tofacitinib who were older than 50 years and had at least one cardiovascular risk factor; **these serious events have not been observed in clinical trials for ulcerative colitis**. There have been rare reports of tears (perforations) in stomach or intestines, serious allergic reactions, and changes in certain lab test results.

S1P Receptor Modulator

Ozanimod (Zeposia[®]) and Etrasimod (Velsipity[™]), sphingosine 1-phosphate (S1P) receptor modulators, are oral small molecule drugs FDA- approved for the treatment of moderate-to-severe ulcerative colitis in adults. S1P receptor modulators work by preventing the migration of immune cells from the lymph nodes to the intestines where they cause inflammation in ulcerative colitis.

Side Effects/Safety

Common side effects:

- *Ozanimod*: Upper respiratory tract infections (common cold, sinus infections), elevated liver enzymes, headache, low blood pressure (when you stand up), and alterations in pulmonary function testing.
- *Etrasimod*: Infections, elevated liver enzymes, headache, and dizziness.

Risks/Safety:

- Taking ozanimod may include risk of serious infections, progressive multifocal leukoencephalopathy (PML), abnormal heart rhythms, including heart block, and fluid build-up in the retina that can cause vision problems. Before you start ozanimod, your physician may request an electrocardiogram (EKG) and/or consultation with a cardiologist. In addition, some patients may require an eye exam with an ophthalmologist.
- Do not take Etrasimod if in the last 6 months you experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure or have or have had a history of unusual heartbeats (arrhythmia) that is not corrected by a pacemaker.

Special Considerations

- Targeted synthetic small molecule medications reduce the activity of the immune system. In so doing, they also decrease the body's ability to fight infections. Be sure to report any signs of infection, including fever, chills, night sweats, sore throat, and other similar symptoms, to your doctor.
- While on one of these medications, it is important to be vaccinated against infections that are preventable. You must, however, avoid live vaccines while you are on one of these agents. There may be an increased risk of zoster (shingles) associated with targeted small molecule medications; all individuals should consider receiving a 2-dose inactivated shingles vaccine series, which is not a live vaccine.
- Prior to starting these medications, your healthcare team will request blood work. Blood work that will be collected may include blood counts to look for anemia or a low white blood cell count, chronic infections, such as tuberculosis (TB) and hepatitis B, liver and kidney function tests, and cholesterol levels.
- There is insufficient data with these medications to establish a risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Women who are pregnant or wish to become pregnant should talk to their doctors before starting targeted small molecule medications. Contraception is recommended during treatment and up to 4 weeks post discontinuation of these medications.
- Become an active participant in your care! Learn as much as possible about these treatments from your doctor and/or pharmacist. Other information can be obtained from reliable sources, such as the Crohn's & Colitis Foundation (www.crohnscolitisfoundation.org) and treatment manufacturer websites.

Combination Therapy

For patients with IBD, these targeted synthetic small molecule medications are used as individual therapy and have not been studied in combination with certain immunosuppressant medications. Combination therapy with another immunomodulators or biologics is not routinely recommended. Steroids should be tapered shortly after starting your medication.

Drug Interactions

Taking several different medicines, whether prescription or over-the-counter, together may cause interactions. Drug interactions may change how well a medication works, or cause unexpected side effects, some more harmful than others. Before taking any medication, be sure to read the label carefully and take it exactly as prescribed. Also, ask your doctor and pharmacist if there are any interactions to note with your existing medications. Be sure to include over-the-counter medications and complementary therapies (supplements, herbals, vitamins, etc.) when discussing your medications. If you are taking ozanimod, it is recommended that you avoid foods that are rich in tyramine (do not consume >150 g). These include aged cheese, fermented foods, including wines, beers, sauerkraut, fish sauce and soy sauce.

Take Medications as Prescribed

The best way to control IBD is by taking medications as recommended by your doctor. Even during periods of remission, it is important to continue taking your medications as prescribed to stay well, and to prevent ongoing inflammation and future disease related complications. If you are experiencing unpleasant side effects or continue to have IBD symptoms, do not stop taking your medications until speaking with your doctor. Do not alter the amount of medication or how frequently you take it on your own.

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October 2023