IMPORTANT SAFETY INFORMATION and INDICATION

Contraindications

- Patients in the last 6 months who experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
- Patients with a history or presence of Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker

Infections

VELSIPITY may increase the susceptibility to infections. Life-threatening and rare fatal infections have been reported in association with other sphingosine 1-phosphate (S1P) receptor modulators. Before starting VELSIPITY, obtain a recent (i.e., within 6 months) CBC, including lymphocyte count. Delay initiation of VELSIPITY in patients with an active infection until the infection is resolved. Consider interruption of treatment with VELSIPITY if a patient develops a serious infection.

- **Progressive multifocal leukoencephalopathy (PML)** is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and usually leads to death or severe disability. PML has been reported in multiple sclerosis (MS) patients treated with S1P receptor modulators. If PML is suspected, suspend VELSIPITY and discontinue if PML is confirmed by appropriate diagnostic evaluation. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients with MS treated with S1P receptor modulators who developed PML and discontinued treatment. Clinical decline may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic MRI changes. Onset was generally within a few months after S1P receptor modulator discontinuation. Monitoring for IRIS should be undertaken.
- **Herpes simplex encephalitis, varicella zoster meningitis, and localized herpes viral infections** have been reported with S1P receptor modulators. In UC-1, herpes zoster was reported in 0.7% of subjects treated with VELSIPITY and in none of the subjects who received placebo. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating VELSIPITY. A full course of VZV vaccination for antibody-negative patients is recommended prior to commencing treatment with VELSIPITY.
- Cases of fatal **cryptococcal meningitis (CM) and disseminated cryptococcal infections** have been reported with S1P receptor modulators. VELSIPITY treatment should be suspended until a cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
- VELSIPITY has not been studied in combination with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies. Avoid concomitant administration of these therapies with VELSIPITY.
- Avoid the use of live attenuated vaccines during and for 5 weeks after treatment with VELSIPITY. If live attenuated vaccine immunizations are required, administer at least 4 weeks prior to initiation of VELSIPITY.

Bradyarrhythmia and Atrioventricular (AV) Conduction Delays

Initiation of VELSIPITY may result in a transient decrease in heart rate and AV conduction delays. Before starting VELSIPITY, obtain an ECG to assess for preexisting cardiac conduction abnormalities.

Liver Injury

Elevations of aminotransferases may occur in patients receiving VELSIPITY. Obtain transaminase and bilirubin levels, if not recently available (i.e., within the last 6 months), before initiation of VELSIPITY or in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue VELSIPITY if significant liver injury is confirmed. Use of VELSIPITY in patients with severe hepatic impairment is not recommended.

Macular Edema

S1P receptor modulators have been associated with an increased risk of macular edema. Obtain baseline evaluation of the fundus, including the macula near the start of VELSIPITY treatment. Periodically assess the fundus, including the macula, during treatment or if there is a change in vision. Consider discontinuing VELSIPITY if macular edema develops.

Increased Blood Pressure
VELSIPITY patients in clinical trials had average increases of 1 to 4 mm Hg systolic and 1 to 2 mm Hg diastolic blood pressure (BP). Increases were first detected after 2 weeks of treatment and remained within the specified average range of BP increases throughout treatment. Monitor BP during treatment with VELSIPITY and manage appropriately.

Fetal Risk
Based on animal studies, VELSIPITY may cause fetal harm. Advise pregnant females and females of reproductive potential of the potential risk to a fetus and to use effective contraception to avoid pregnancy during and for one week after stopping VELSIPITY. Pregnant females exposed to VELSIPITY are encouraged to contact the pregnancy registry by calling 1-800-616-3791.

Malignancies
Cases of malignancies (including skin) have been reported in patients treated with S1P receptor modulators. Skin examinations are recommended prior to or shortly after the start of treatment and periodically thereafter for all patients, particularly those with risk factors for skin cancer. Monitor for suspicious skin lesions.

Posterior Reversible Encephalopathy Syndrome
Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving S1P receptor modulators. If a patient develops neurological or psychiatric symptoms/signs or any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, complete a physical and neurological examination promptly and consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, discontinue treatment with VELSIPITY.

Respiratory Effects
VELSIPITY may cause a decline in pulmonary function. Spirometric evaluation should be conducted during therapy if clinically indicated.

Unintended Additive Immune System Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Drugs
When switching to VELSIPITY from drugs with prolonged immune effects, consider the half-life and mode of action of these drugs to avoid unintended additive immunosuppressive effects.

Immune System Effects After Stopping VELSIPITY
After stopping VELSIPITY, lymphocyte counts returned to the normal range in 90% of subjects within 4 to 5 weeks. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore monitor patients receiving concomitant immunosuppressants for infectious complications up to 5 weeks after the last dose of VELSIPITY.

Most Common Adverse Reactions
Most common adverse reactions reported in ≥ 2% of subjects and at a higher rate than placebo included: headache, elevated liver tests, dizziness, arthralgia, nausea, hypertension, bradycardia, UTI, hypercholesterolemia, and herpes viral infection.

INDICATION
VELSIPITY is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults.

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