

# FULL FAIR BALANCE

## Important Safety Information

### Indication

- TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- $\alpha$
- In CD, TYSABRI should not be used in combination with immunosuppressants or inhibitors of TNF- $\alpha$

### Contraindications

- TYSABRI is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML)
- TYSABRI should not be administered to a patient who has had a hypersensitivity reaction to TYSABRI. Observed reactions range from urticaria to anaphylaxis

### WARNINGS AND PRECAUTIONS

- **TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking TYSABRI who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving TYSABRI monotherapy**
- **Because of the risk of PML, TYSABRI is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program**
- **Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended**

### Progressive Multifocal Leukoencephalopathy (PML)

- Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus that typically occurs in patients who are immunocompromised, developed in three patients who received TYSABRI in clinical trials
- Two cases of PML were observed among 1869 patients with multiple sclerosis (MS) treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease (CD) after the patient received 8 doses. Both MS patients were receiving concomitant immunomodulatory therapy and the CD patient had been treated in the past with immunosuppressive therapy.
- In the postmarketing setting, additional cases of PML have been reported in MS patients who were receiving no concomitant immunomodulatory therapy
- The absolute risk for PML in patients treated with TYSABRI cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified
- There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs
- It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease
- There is limited experience beyond 2 years of treatment. The relationship between the risk of PML and the duration of treatment is unknown but most cases of PML were in patients who received more than one year of treatment

- Ordinarily, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI
- The incidence of PML appears to be lower in patients receiving TYSABRI as monotherapy; however, the number of cases is too few and the number of patients treated too small to reliably conclude that the true risk of PML is lower in patients treated with TYSABRI alone than in patients who are receiving other drugs that decrease immune function or who are otherwise immunocompromised
- Because of the risk of PML, TYSABRI is available in the US only through a special restricted distribution program, the TOUCH™ Prescribing Program
- In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on TYSABRI therapy are uncommon
- Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Withhold TYSABRI dosing immediately at the first sign or symptom suggestive of PML
- For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended

### Hypersensitivity/Antibody Formation

- Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%
- These reactions usually occur within 2 hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain
- Generally, these reactions are associated with antibodies to TYSABRI
- If a hypersensitivity reaction occurs, administration of TYSABRI should be discontinued and appropriate therapy initiated. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI
- The possibility of antibodies to TYSABRI should be considered in patients who have hypersensitivity reactions
- Antibody testing: If the presence of persistent antibodies is suspected, antibody testing should be performed. Antibodies detected early in the treatment course (e.g., within the first six months) may be transient and disappear with continued dosing. Repeat testing at three months after the initial positive result is recommended in patients in whom antibodies are detected to confirm that antibodies are persistent. Prescribers should consider the overall benefits and risks of TYSABRI in a patient with persistent antibodies

### Immunosuppression/Infections

- The immune system effects of TYSABRI may increase the risk for infections
- In clinical studies for CD, opportunistic infections (*pneumocystis carinii pneumonia*, *pulmonary mycobacterium avium intracellulare*, *bronchopulmonary aspergillosis*, and *burkholderia cepacia*) have been observed in <1% of TYSABRI-treated patients; some of these patients were receiving concurrent immunosuppressants
- In Studies CD1 and CD2, an increase in infections was seen in patients concurrently receiving corticosteroids. However, the increase in infections was similar in placebo-treated and TYSABRI-treated patients who received steroids
- Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI alone
- The safety and efficacy of TYSABRI in combination with antieoplastic, immunosuppressant, or immunomodulating agents has not been established

- Patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not ordinarily be treated with TYSABRI
- For patients with Crohn's disease who start TYSABRI while on chronic corticosteroids, commence steroid withdrawal as soon as a therapeutic benefit has occurred. If the patient cannot discontinue systemic corticosteroids within 6 months, discontinue TYSABRI
- In Studies CD1 and CD2, the rate of any type of infection was 1.7 per patient-year in TYSABRI-treated patients and 1.4 per patient-year in placebo-treated patients. The most common infections were nasopharyngitis, upper respiratory tract infection, and influenza
- The majority of patients did not interrupt TYSABRI therapy during infections and recovery occurred with appropriate treatment
- Concurrent use of TYSABRI in CD clinical trials with chronic steroids and/or methotrexate, 6-MP, and azathioprine was not associated with an increase in infection compared to TYSABRI alone; however, the concomitant use of such agents could lead to an increased risk of infection
- In Studies CD1 and CD2, the incidence of serious infection was approximately 2.1% in both TYSABRI-treated patients and placebo-treated patients
- In Study CD3, the incidence of serious infection was approximately 3.3% in TYSABRI-treated patients and approximately 2.8% in placebo-controlled patients
- Two serious non-bacterial meningitides cases occurred in TYSABRI-treated patients compared to none in placebo-treated patients

### Hepatotoxicity

- Clinically significant liver injury has been reported in patients treated with TYSABRI in the postmarketing setting. In some patients, liver injury recurred upon rechallenge, providing evidence that TYSABRI caused the injury
- The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients
- TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence)

### Additional Safety Considerations

- The following serious adverse events in the induction Studies CD1 and CD2 were reported more commonly with TYSABRI than placebo and occurred at an incidence of at least 0.3%: intestinal obstruction or stenosis (2% vs 1% in placebo), acute hypersensitivity reactions (0.5% vs 0%), abdominal adhesions (0.3% vs 0%), and cholelithiasis (0.3% vs 0%)
- An infusion-related reaction was defined in clinical trials as any adverse event occurring within 2 hours of the start of an infusion. In Studies CD1 and CD2, infusion-related reactions occurred in approximately 11% of patients treated with TYSABRI compared to 7% of placebo-treated patients. Infusion-related reactions more common in CD patients receiving TYSABRI than those receiving placebo included headache, nausea, urticaria, pruritus, and flushing. Serious infusion reactions occurred in Studies CD1, CD2, and CD3 at an incidence of <1% in TYSABRI-treated patients.
- TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman becomes pregnant while taking TYSABRI, consider enrolling her in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255
- Safety and effectiveness of TYSABRI in pediatric patients with Crohn's disease below the age of 18 years have not been established. TYSABRI is not indicated for use in pediatric patients
- Clinical studies of TYSABRI did not include sufficient numbers of patients aged 65 years and over to determine whether they responded differently than younger patients