

הודעה על החמרה (מידע בטיחות)

תאריך: 01.02.12

שם תכשיר באנגלית: Tysabri

מספר רישום: 136 45 31505 00

שם בעל הרישום: Medison Pharma Ltd.

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינויים המבוקש/ים		
טקסט חדש	טקסט נוכחי	פרק בעלון
<p>Progressive Multifocal Leukoencephalopathy (PML) Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, developed in three patients who received TYSABRI in clinical trials [see <i>Boxed Warning</i>]. Two cases of PML were observed among 1869 patients with multiple sclerosis treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease after the patient received eight doses. Both multiple sclerosis patients were receiving concomitant immunomodulatory therapy and the Crohn's disease patient had been treated in the past with immunosuppressive therapy.</p> <p>In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis and Crohn's disease patients who were receiving no concomitant immunomodulatory therapy. <u>Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified:</u></p> <ul style="list-style-type: none"> • <u>Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment.</u> • <u>Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).</u> 	<p>טקסט נוכחי <u>Progressive Multifocal Leukoencephalopathy (PML)</u></p> <p>Use of TYSABRI has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist physician and the patient.</p> <p>Patients should be instructed together with their caregivers on early signs and symptoms of PML.</p> <p>Each of the following independent risk factors is associated with an increased risk of PML.</p> <ul style="list-style-type: none"> • Treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment therefore the risk of PML in these patients cannot currently be estimated. • Immunosuppressant use prior to receiving TYSABRI. • The presence of anti-JCV antibodies. <p>Anti-JCV antibody status identifies different levels of risk for PML in TYSABRI treated patients. Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., have received more than 2 years of TYSABRI therapy, and have received prior immunosuppressant therapy and are anti-JCV antibody positive) have the highest risk of PML at approximately 9 in 1,000 patients treated. Patients should be informed about this increased risk for developing PML before continuation of treatment after 2 years.</p> <p>For risk stratification prior or during the treatment with TYSABRI anti-JCV antibody</p>	<p>פרק בעלון</p> <p>4.4 Special Warnings and precautions for use</p>

- The presence of anti-JCV antibodies.

Patients who are anti-JCV antibody positive have a higher risk for developing PML.

The risks and benefits of continuing treatment with Tysabri should be carefully considered in patients who are found to be anti-JCV antibody positive and have one or more additional risk factors. Patients with all three known risk factors have an estimated risk of PML of 11/1,000.

Consideration should be given to testing patients for anti-JCV antibody status prior or during treatment if antibody to treatment status is unknown. Infection by the JC virus is required for the

development of PML. Anti-JCV antibody negative status indicates that exposure to the JC virus has not been detected. Patients who are anti-JCV antibody negative are still at risk for the development of PML due to the potential for a new JCV infection or a false negative test result.

Therefore, patients with a negative anti-JCV antibody test result should be retested periodically.

For purposes of risk assessment, a patient with a positive anti-JCV antibody test at any time is considered anti-JCV antibody positive regardless of the results of any prior or subsequent anti-JCV antibody testing. When assessed, anti-JCV antibody status should be determined using an analytically and clinically validated immunoassay.

Table 1: Estimated Incidence of PML Stratified by Risk Factor

Tysabri Exposure†	Anti-JCV Antibody Positive*	
	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1-24 months	<1/1,000	2/1000
25-48 months	4/1000	11/1000

Notes: Based on postmarketing PML data and Tysabri use data as of September 1, 2011.

†Data beyond 4 years of treatment are limited.

*Risk in anti-JCV antibody positive patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated MS patients are anti-JCV antibody positive.

The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically

testing may provide supportive information.

Before initiation of treatment with TYSABRI, a recent (usually within 3 months) MRI should be available as a reference, and be repeated on a yearly routine basis to update this reference. Patients must be monitored at regular intervals throughout. After 2 years the patient should be re-informed about the risk of PML with TYSABRI.

If PML is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are typical of MS or possibly suggestive of PML. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines (see educational guidance). Once the clinician has excluded PML (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing of natalizumab may resume.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML the dosing of TYSABRI must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML improved outcome has been seen.

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all TYSABRI PML patients after withdrawal or removal of TYSABRI, e.g. by plasma exchange (see section 5.2). IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS, which has occurred within days to several weeks after plasma exchange in TYSABRI treated patients with PML, and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with a false negative rate of 3%.

Anti-JCV antibody testing should not be used to diagnose PML.

Anti-JCV antibody testing should not be performed for at least two weeks following plasma exchange due to the removal of antibodies from the serum.

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.

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.

Because of the risk of PML, TYSABRI is available only under a special restricted distribution program, the TOUCH® Prescribing Program.

In multiple sclerosis patients, an MRI scan should be obtained prior to initiating therapy with TYSABRI. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.

Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. Withhold TYSABRI dosing immediately at the first sign or symptom suggestive of PML.

For diagnosis of PML, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended. If the initial evaluations for PML are negative but clinical suspicion for PML remains, continue to withhold TYSABRI dosing and repeat the evaluations.

There are no known interventions that can adequately treat PML if it occurs. Three sessions of plasma exchange over 5 to 8 days were shown to accelerate TYSABRI clearance in a study of 12 patients with MS who did not have PML, although in the majority of patients alpha-4 integrin receptor binding remained high. Adverse events which may occur during plasma exchange include clearance of other medications and volume shifts, which have the potential to lead to hypotension or pulmonary edema. Although plasma exchange has not been studied in TYSABRI treated patients with PML, it has been used in such patients in the postmarketing setting to remove TYSABRI more quickly from the circulation. Anti-JCV antibody testing should not be performed during or for at least two weeks following plasma exchange due to the removal of antibodies from the serum. Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI treated patients who developed PML and subsequently discontinued TYSABRI. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating TYSABRI. It presents as a clinical decline in the patient's condition after TYSABRI removal (and in some cases after apparent clinical improvement) that may be rapid, can lead to serious neurological complications or death and is often associated with characteristic changes in the MRI. TYSABRI has not been associated with IRIS in patients discontinuing treatment with TYSABRI for reasons unrelated to PML. In TYSABRI-treated patients with PML, IRIS has been reported within days to several weeks after plasma exchange. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken. 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. Ordinarily, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised

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העלון, שבו מסומנים השינויים המבוקשים על רקע צהוב הועבר בדואר אלקטרוני בתאריך 01.02.12

קיים עלון לצרכן והוא מעודכן בהתאם.

אסמכתא לבקשה: <http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm>

השינוי הנ"ל אושר על ידי רשויות הבריאות ב-USA

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חתימת הרוקח הממונה