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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), CENTER FOR MEDICATION SAFETY (VA MEDSAFE), & MS CENTERS OF EXCELLENCE

NATALIZUMAB (TYSABRI ®) AND THE RISK OF DEVELOPING PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) AND IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

I. ISSUE [1]

The U.S. Food and Drug Administration (FDA) has requested updates to the natalizumab (Tysabri®) drug label and to the patient *Medication Guide* as follows:

- The risk of developing progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection associated with the use of Tysabri® (natalizumab), increases with the number of Tysabri® infusions received.
- Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported in patients who discontinue natalizumab due to developing PML. Symptoms of IRIS include a severe inflammatory response that can occur while the immune system is recovering. Because of this, a patient's condition may unexpectedly decline despite improved immune function.

II. BACKGROUND [1]

- In November 2004, FDA approved natalizumab (Tysabri®) for the treatment of relapsing forms of multiple sclerosis (MS).
- In February 2005, the manufacturer temporarily withdrew natalizumab (Tysabri®) from the market because of the occurrence of three cases of PML (two patients in MS trials and one in a Crohn's disease [CD] trial).
- In June 2006, marketing resumed, and from July 2006 through January 21, 2010, 31 cases of PML were confirmed worldwide.
  - 10 (out of 31) cases were from the U.S.
  - 8 (out of 31) patients have died as of January 21, 2010.
  - In all cases, patients were receiving natalizumab (Tysabri®) as monotherapy for the treatment of MS.
- The risk of developing PML increases with the number of natalizumab (Tysabri®) infusions received. The table below shows cumulative rates of PML according to geographic location and number of infusions received since re-marketing:

Number of Tysabri infusions received	Overall cumulative rate of PML per 1,000 patients	Cumulative rate of PML per 1,000 patients outside of U.S.	Cumulative rate of PML per 1,000 patients in U.S.
≥ 1	0.5	0.7	0.3
≥ 12	0.8	1.1	0.5
≥ 24	1.3	1.9	0.8
≥ 30	1.0	1.8	0.5

III. PROVIDER RECOMMENDATIONS [1]

- As recommended by the FDA,
  - *Natalizumab (Tysabri®) should be withheld at the first sign or symptom suggestive of PML.*
  - *Continued clinical vigilance and close monitoring for the signs and symptoms of PML as dictated by the Tysabri® Outreach Unified Commitment to Health (the TOUCH™ Prescribing Program) is necessary.*

- *Healthcare professionals should monitor their patients for the development of IRIS and appropriate treatment of the associated inflammation after stopping natalizumab (Tysabri®) should be undertaken.*

- VA Providers must complete initial registry forms prior to natalizumab initiation in VA. Providers are strongly encouraged to submit annual update forms to the MSCoE Registry.
  http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Criteria%20For%20Use/Natalizumab%20MSCoE%20Initial%20Registry8_09.docx

  http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Criteria%20For%20Use/Natalizumab%20MSCoE%20Annual%20Registry%2008_09.doc

IV. REFERENCES

1. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199872.htm . (Accessed 2-05-10)

ACTIONS:

- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g.,* ***primary care providers, neurologists, physical medicine and rehabilitation (PM&R), and GI specialists,*** *including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*