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DEPARTMENT OF VETERANS AFFAIRS - VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND
CENTER FOR MEDICATION SAFETY PSCI (VA MedSAFE),

Cases of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with CellCept® (mycophenolate mofetil).

I. ISSUE

The Food and Drug Administration (FDA) and Roche laboratories have announced the addition of a black boxed warning to the product labeling for Cellcept® (mycophenolate mofetil) highlighting postmarketing data on the development of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with CellCept® (mycophenolate mofetil). PML is an infection of the brain that is sometimes fatal and has been reported in patients treated with Cellcept®. The reported cases generally had additional risk factors for PML, including treatment with additional immunosuppressant therapies.

II. BACKGROUND

On April 10, 2008 the FDA announced it was investigating a potential association between the use of CellCept® and Myfortic®, and the development of PML. The FDA reviewed data submitted by Roche, including postmarketing reports it has received of PML in patients who took CellCept® or Myfortic®, and the proposed revisions to the CellCept® prescribing information. The FDA has asked Novartis, the maker of Myfortic®, for data on PML cases and to revise the Myfortic® prescribing information to include the same information about PML included in the CellCept® prescribing information.

III. DISCUSSION

There have been 17 cases of PML reported to Roche via post marketing surveillance. Of these cases, seven had a fatal outcome, five improved and five had an unknown outcome or the event was ongoing at the time of the report. Ten of the PML cases were confirmed by detection of the JC virus in the cerebrospinal fluid or by brain biopsy. Of these cases, six were solid organ recipients and four were systemic lupus erythematosus patients (SLE). There were six possible cases (no JC virus confirmation) of PML, four of these patients were solid organ recipients and two were SLE patients. The seventh possible case was an HIV positive patient. Both the transplant patients and SLE patients were receiving other concomitant immunosuppression.

IV. VA MEDSAFE RECOMMENDATIONS *reinforce those of the FDA and include:*

- Patients receiving immunosuppressive regimens involving multiple immunosuppressive agents are at an increased risk of developing opportunistic infections and sepsis.
- In an immunosuppressed patient, physicians should consider PML in the differential diagnosis in patients presenting with neurologic symptoms. In the reported cases of PML the most frequently observed clinical symptoms were; hemiparesis, apathy, confusion, cognitive deficiencies and ataxia.
- The post marketing reports for Myfortic® (mycophenolic acid) and PML have not been reviewed or included in this report. However, in its initial investigation the FDA requested that the prescribing information be the same for both agents.
- Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In solid organ transplant recipients this reduction in immunosuppression would have to be evaluated with the risk of graft rejection.
- Providers should document/report all possible adverse events related to mycophenolate mofetil/ mycophenolic acid use as per the usual protocols used at their VA.
- Further information regarding the revised package labeling for Cellcept® can be accessed via the following link: http://rocheusa.com/products/cellcept/CellceptLetterPML_May2008.pdf