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Leukotriene Inhibitors [Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR)] and Neuropsychiatric Events

- In April 2009, the Food and Drug Administration (FDA) reviewed post-marketing reports and clinical trial data on mood and behavioral changes associated with the use of leukotriene inhibitors. [1]
- Neuropsychiatric events reported in patients taking montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR) include[1]:
  - Agitation
  - Aggression
  - Anxiousness
  - Dream abnormalities and hallucinations
  - Depression
  - Insomnia
  - Irritability
  - Restlessness
  - Suicidal thinking and behavior (including suicide)
  - Tremor.
- FDA has requested that manufacturers revise the drug prescribing information to include a precaution addressing the above events.
- Limited literature exists regarding suicidality and leukotriene inhibitors.[2, 3]
  - One study reviewed available reports of suicidality and treatment of allergy with leukotriene inhibitors and found insufficient data associating montelukast with suicidality. [2]
  - Another population-based cohort study showed no cases of suicide in patients receiving montelukast during the study time period. [3]
    - 23,500 patients received over 250,000 montelukast prescriptions from February 1998 – March 2007.
    - No cases of suicide were identified.
- FDA recommends[1]:
  - *Patients and healthcare professionals should be aware of the potential for neuropsychiatric events with these medications.*
  - *Patients should talk with their healthcare providers if these events occur.*
  - *Healthcare professionals should consider discontinuing these medications if patients develop neuropsychiatric symptoms.*
- VA Center for Medication Safety (VAMedSAFE) will monitor and analyze reports of adverse events with leukotriene inhibitors to better characterize the adverse event profile in the veteran population.

REFERENCES:

1. FDA.http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm. (Accessed June 12, 2009).
2. Manalai P, Woo JM, Postolache TT. Suicidality and montelukast. *Expert Opin Drug Saf*. 2009 May; 8(3):273-282.
3. Jick H, Hagberg KW, Egger P. Rate of suicide in patients taking montelukast. *Pharmacotherapy*. 2009 Feb; 29(2):165-166.

ACTIONS

- ***Facility Director (or physician designee):*** *Report completion of actions to the VISN Director.*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g.,* ***primary care providers, pulmonologists, allergy-immunology providers, and head and neck surgeons,*** *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. Report completion of actions to the Facility Director.*
- ***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).*
- ***VISN Directors:*** *Within 10 business days of receipt (due 06/29/2009), communicate to PBM/VAMedSAFE that all actions have been completed via the Feedback tool: http://vaww.national.cmop.va.gov/PBM/visn_drug_recalls_alerts/default.aspx.*