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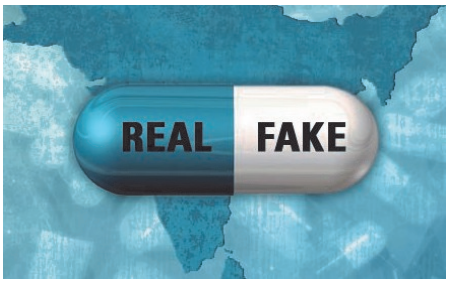
Medication safety in seconds

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use



BEVACIZUMAB (AVASTIN®): COUNTERFEIT VIALS (400MG/16ML) IN U.S. DISTRIBUTION

Bevacizumab (Avastin®), a monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A), received initial FDA approval in 2004. This agent is indicated for the treatment of metastatic cancers (colorectal, breast, lung [non-squamous non-small cell], and renal) as well as glioblastoma.[1] Off-label use for macular degeneration and other vascular eye conditions has become a common practice as these conditions involve proliferation of blood vessels in the retina.

FDA warns of counterfeit vials of bevacizumab (Avastin®) 400mg/16mL distributed in the United States. The counterfeit versions have labeling that displays the product as Avastin, manufactured by Roche, but does not contain the medicine's active ingredient (bevacizumab), as confirmed by laboratory tests conducted by Roche. This could result in patients not receiving adequate chemotherapy and optimum benefit.

The counterfeit packages and vials have labels that display:

- Roche as the manufacturer;
- Batch numbers that start with B6010, B6011, or B86017;
- French language.

FDA identified Quality Specialty Products (QSP), also known as Montana Health Care Solutions, as the supplier of the counterfeit bevacizumab (Avastin®). A company called Volunteer Distribution in Ganiesboro, Tennessee, distributes QSP's products.

While Roche manufactures bevacizumab (Avastin®) for marketing outside of the United States, Genentech (a subsidiary of Roche) markets the only FDA-approved version of bevacizumab (Avastin®) for use in the United States. The FDA-approved product does not show a Roche logo on the packaging or vials. According to the FDA, no shortage of bevacizumab (Avastin®) exists, and current supplies adequately meet demand. [2] VA has not been affected by this counterfeit supply.

REFERENCES

1. Avastin® (bevacizumab) [package insert]. South San Francisco, CA: Genentech, Inc.; September 2011.
2. FDA Drug Safety and Availability: Counterfeit Version of Avastin in U.S. Distribution. http://www.fda.gov/Drugs/DrugSafety/ucm291960.htm (Accessed 02/16/12).

NEWS YOU CAN USE

FROM THE VA NATIONAL PBM: BULLETINS, COMMUNICATIONS, & RECALLS

- Aliskiren: Adverse Drug Events When Concomitantly Used with ACE Inhibitors or ARBs in Patients with Type II DM - National PBM Communication – 01/13/2012
- Dronedarone and Cardiovascular Events in Permanent Atrial Fibrillation - National PBM Communication – 01/10/2012

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NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

Tysabri - New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab)

01/20/2012

As of January 2012, PML has developed in 201 out of approximately 96,582 patients treated with Tysabri worldwide. The risks and benefits of Tysabri treatment should be carefully considered in patients with risk factors for PML, which now include:

- The presence of anti-JCV antibodies. (*NEW*)
  - An analytically and clinically validated anti-JCV antibody detection test ordered by a healthcare professional (i.e., the Stratify JCV Antibody ELISA test) can determine a patient's anti-JCV antibody status.
  - Patients negative for anti-JCV antibodies can still develop PML due to the potential for a false negative test result or a new JCV infection.
- Extended duration of Tysabri treatment (i.e., beyond 2 years).
- Prior immunosuppressive drug therapy (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil).

Patients with all three known risk factors have an estimated risk of PML of 11/1,000. Updates to the Tysabri label will include new information on the estimated PML incidence stratified by risk factor.

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

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 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%.*

Adcetris - New Boxed Warning and Contraindication for Adcetris (brentuximab vedotin)

01/13/2012

- *Progressive multifocal leukoencephalopathy (PML) - New boxed warning on product label highlights risk as additional cases surface.*
  - To date, three patients developed PML while receiving treatment with Adcetris (two recent as per above and one documented in the Warnings and Precautions section of the label at the time of approval in August 2011).
    - A 48 year old man with Hodgkin's lymphoma (HL) [whose past medical history included treatment with multiple chemotherapeutic agents and targeted radiation therapy] presented with left-sided weakness and slurred speech after the third dose of Adcetris. Cerebrospinal fluid was positive for John Cunningham (JC) virus. The patient died within four weeks of onset of symptoms.
    - A 50 year old man with HL (whose past medical history included prior treatment with multiple chemotherapeutic agents, targeted radiation therapy, and autologous stem cell transplant) presented to the local emergency room with complaints of changes in speech, difficulty writing with his right hand, right lower extremity weakness, poor coordination, poor balance, and left-sided sensory deficits after receiving eight cycles of Adcetris treatment. An immunostain of a spinal cord lesion biopsy was positive for JC virus. The patient continued to deteriorate, with recent loss of lower extremity motor function and deep tendon reflexes. He also experienced hand tremors and hypoactive arm reflexes.
    - A 38 year old female patient with a history of Stage IV cutaneous anaplastic large cell lymphoma (ALCL) [whose past medical history included prior treatment with multiple chemotherapeutic agents and targeted radiation therapy] complained of inability to read, inability to find words to express herself, memory lapses, and slight loss of balance after the second dose of Adcetris. A brain MRI revealed demyelination and JC virus appeared on brain biopsy. Treatment with Adcetris was discontinued.
- *Pulmonary toxicity - New contraindication on product label prohibits Adcetris use with bleomycin due to risk of pulmonary toxicity.*
  - A clinical trial comparing the combination of Adcetris plus Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD) to the combination of Adcetris plus Adriamycin (doxorubicin), vinblastine, and dacarbazine (AVD) as front-line therapy for HL showed that an excessive number of patients in the Adcetris plus ABVD treatment group experienced non-infectious pulmonary toxicity (approximately 40%, compared to a frequency of 10-25% reported in the literature with bleomycin-based regimens that do not contain Adcetris).
  - No pulmonary toxicity has occurred thus far in the Adcetris plus AVD treatment group.

CardioGen-82 - Update: Preliminary findings from ongoing investigations of CardioGen-82

01/12/2012 (***UPDATE FROM 07/26/2011***)

FDA states that substandard manufacturing procedures for CardioGen-82 did not result in the excessive radiation exposure detected in some patients as previously thought. None of the recalled CardioGen-82 generators that had undergone testing for structural or functional inadequacies showed signs of strontium breakthrough. Preliminary data from a manufacturer study reveals that out of 375 patients surveyed at 43 clinical sites, 54 patients (from 2 clinical sites [recognized as having poor documentation of compliance for recommended strontium breakthrough testing]) reported abnormal screening test results. FDA continues to work with the manufacturer to assess possible causes for excessive radiation exposure in patients at certain clinical sites.

Getting the most from our safety surveillance

DIAZEPAM AND DILTIAZEM | POTENTIAL LOOK-ALIKE (LA)/SOUND-ALIKE (SA) CONFUSION

Two VA medical centers reported an LA/SA error between diltiazem and diazepam secondary to nursing staff withdrawing the wrong medication from the automated dispensing system in the emergency department (ED). In one instance, typing "DI" into the automated dispensing system listed "DIAZEPAM" first, which staff inadvertently pulled from the machine and injected into the patient instead of the intended diltiazem. The nurse realized the administration of the incorrect diazepam and notified the physician, who subsequently ordered and administered flumazenil to counter its effects. The patient remained in the ED for monitoring with no adverse events reported. A root-cause analysis is pending. In the other case, the facility took corrective action by requiring verification by a witness whenever retrieving diazepam from the automated dispensing system.

Diazepam and diltiazem is not a medication name pair recognized by the Institute for Safe Medication Practices (ISMP) as having the potential for look-alike/sound-alike (LA/SA) confusion. Diazepam is a benzodiazepine used in the treatment of anxiety, muscle spasms, seizures, and symptoms of alcohol withdrawal. Diltiazem is a calcium-channel blocker used in the treatment of cardiovascular issues, such as hypertension and/or elevated heart rate. Incorrectly receiving diazepam instead of diltiazem in the ED would subject the patient to suboptimal blood pressure and/or heart rate control in a critical setting, while introducing the risks of possible exposure to patients with contraindications to diazepam (i.e., patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, sleep apnea syndrome, and acute narrow angle glaucoma) or other risk factors that may preclude its use (concomitant use of agents that may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants; history of drug abuse and dependence). The risk of a benzodiazepine overdose (i.e., respiratory depression) also increases due to the difference in product strengths and dosing. On the other hand, patients inadvertently administered diltiazem instead of diazepam may experience hypotension and/or a possible decrease in heart rate without receiving urgently needed anxiolytic, muscle relaxant, sedative, or anticonvulsant effects.

REFERENCES

1. Field Information Report.
2. ISMP's List of Confused Drug Names. June 2011. Horsham, PA: Institute of Safe Medication Practices. Available at: http://ismp.org/tools/confuseddrugnames.pdf . (Accessed 02/01/2012).

PROVIDER RECOMMENDATIONS:

- Consider informing health care staff of the potential for LA/SA confusion between diazepam and diltiazem when withdrawing these medications via the automated dispensing system, especially if selection of either medication occurs via an alphabetic medication list.
- Consider carefully checking the name, dosage, and indication when either diazepam or diltiazem is ordered, especially if selection of either medication occurs via an alphabetic medication list in the automated dispensing system.
- Consider ensuring that a method is in place to help differentiate the products when using an automated dispensing system to avoid future LA/SA confusion.
- Continue to report any close-calls and/or actual errors involving LA/SA name pair confusion to Muriel.Burk@va.gov .