U.S. Food and Drug Administration
Protecting and Promoting Public Health

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IN THIS ISSUE

THE NEWSLETTER'S MISSION

This publication provides postmarketing information to healthcare professionals to enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting. For more information, visit the FDA Drug Safety Newsletter Fact Sheet at *http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm107474.htm*.

REPORTING ADVERSE EVENTS

FDA encourages the reporting of all suspected adverse drug reactions, drug interactions, and reactions that result in death, life-threatening outcomes, hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defects.

Report serious adverse events to FDA's MedWatch reporting system by completing an online form at *www.fda.gov/medwatch/report.htm*, by faxing (1-800-FDA-0178), by mail using the pre-paid postage address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

EDITOR'S NOTE

In this issue, we describe three drug safety issues. In the first article, we discuss the relative risks associated with using quinine for unapproved indications. Quinine has only been approved for treatment of uncomplicated malaria. Despite several regulatory actions, the discrepancy between the incidence of malaria and large number of quinine prescriptions suggests that off-label quinine use (e.g., for the treatment of leg cramps) remains extensive. FDA continues to receive reports of patients experiencing serious adverse events, including thrombocytopenia, after quinine use.

Second, FDA has received reports of cases of acute renal impairment and failure associated with the use of Reclast (zolendronic acid). Reclast is the first bisphosphonate drug approved by the FDA for once-yearly intravenous treatment for osteoporosis in postmenopausal women. Data suggest there may be a higher risk for renal impairment and acute renal failure for patients who have compromised renal function, are experiencing dehydration, or might be taking concomitant nephrotoxic medications. FDA encourages healthcare professionals to monitor their patients' renal function before and after a Reclast infusion.

Finally, we discuss the adverse event profile of arginine hydrochloride injection (marketed as R-Gene 10), a diagnostic tool used to measure the pituitary reserve for human growth hormone. This drug is mostly used in children to evaluate possible problems in growth and stature. Specifically, in this article we highlight medication errors (unintentional overdoses) that have resulted in serious adverse events, including deaths. This article also summarizes FDA's analysis of non-medication error-related adverse events associated with the use of arginine hydrochloride.

In each *Newsletter*, we bring to your attention a list of medicine-related safety issues. We hope you find the information useful. Feel free to share your comments with us at *http://www.fda.gov/AboutFDA/CentersOffices/CDER/ContactCDER/default.htm*. We also remind healthcare professionals to continue to report serious adverse events to FDA at *www.fda.gov/medwatch/report.htm*.

Renan A. Bonnel, PharmD, MPH
Sr. Scientific Editor

POSTMARKET REVIEWS

QUININE SULFATE (MARKETED AS QUALAQUIN)

Off-label (not approved by FDA) use of quinine

Abstract: Quinine sulfate is approved by the FDA for treatment of uncomplicated *Plasmodium falciparum* malaria, a rare disease in the United States. Drug use data indicate that many prescriptions for quinine sulfate are written in this country, most likely for off-label uses (e.g., the treatment of nocturnal leg cramps). Despite taking several regulatory actions to ensure the safe use of quinine, FDA continues to receive reports of serious adverse events associated with this drug. From April 2005 through October 1, 2008, 38 domestic cases with serious outcomes were reported to FDA's Adverse Event Reporting System (AERS). Most reports were of hematologic events, including cases of thrombocytopenia, and resulted in the hospitalization of the patient. Practitioners should be aware that there are no data indicating that quinine is effective for the treatment of nocturnal leg cramps or other musculoskeletal disorders, and given the potential for life-threatening adverse events, should use extreme caution in off-label prescribing.

Keywords: quinine sulfate, leg cramps, off-label use

In the United States, the annual reported incidence of malaria infections is low and stable.[1,2] Qualaquin (quinine sulfate) is the only FDA-approved quinine product (2005) indicated for the treatment of uncomplicated malaria caused by *P. falciparum*.[3] Despite the low incidence of malaria, there are a large number of prescriptions for quinine dispensed each year. In the first two quarters of 2008, 124,024 patients in the United States received nearly 297,000 prescriptions for Qualaquin.[4] Assuming that the number of malaria cases in the United States remains stable—in 2007, 1,505 U.S. malaria cases were reported to the Centers for Disease Control and Prevention (CDC)—the large number of prescriptions suggests that off-label use of quinine remains extensive.[2]

Quinine products have long been used for the treatment of nocturnal leg cramps, which is not an FDA-approved indication. A recent report notes that, from January 2006 to June 2008, a large proportion of quinine prescriptions (62%) were written for musculoskeletal symptoms, rather than uncomplicated malaria.[5] There are no reliable data supporting the efficacy and safety of quinine for treatment of leg cramps, making the risks associated with such use stand out in comparison to potential benefit. Specifically, using quinine to treat leg cramps may expose patients to substantial and unnecessary risk.

Qualaquin (quinine sulfate) is indicated only for the treatment of uncomplicated *P. falciparum* malaria[3]

Cure rates with 7 days of oral quinine monotherapy in areas where multi-drug resistance is not widespread range from 86% to 100%

The Agency has taken several regulatory actions to minimize the use of quinine for unapproved indications.[6] In December 2006, FDA informed manufacturers to stop marketing unapproved prescription quinine products, citing serious safety concerns, including deaths. FDA has also cautioned consumers about the potential for adverse events with serious outcomes if they take quinine for unapproved indications. These serious outcomes include thrombocytopenia, hypersensitivity reactions, and cardiac dysrhythmias. Following FDA's actions on unapproved quinine products, only one quinine drug, Qualaquin, remained on the market as FDA-approved. The Agency and the manufacturer of this drug implemented risk mitigation strategies that include an educational program for healthcare providers regarding the safe and effective use of quinine sulfate. The manufacturer also issued a *Dear Healthcare Professional Letter* in 2006 to warn healthcare professionals about the risks associated with quinine.

Despite these actions, FDA continues to receive reports of serious adverse events with the use of quinine, most citing off-label use. Specifically, from April 2005 to October 1, 2008, FDA's Adverse Event Reporting System (AERS) received a total of 38 domestic cases of serious adverse events associated with quinine. The majority of patients in this case series (66%) took quinine to prevent or treat leg cramps or Restless Leg Syndrome. Tables 1 and 2 describe the characteristics of all 38 AERS cases.

Among these reports, 24 cases (63%) were for a hematologic event. Four cases (11%) noted that the patient experienced a cardiovascular event. Ten cases (26%) noted that the patient experienced a variety of adverse events, including GI symptoms, hearing loss, rash, electrolyte imbalance, and drug interaction.

For the hematologic events, the median reported time-to-onset after initiation of treatment and median reported quinine dose was 13.5 days and 325 mg/day, respectively. Of these cases, 87.5 % (21/24) had a diagnosis of thrombocytopenia and required hospitalization. Of these 21 cases, 18 provided data on platelet count with 14 reporting a platelet count less than 5000 cells/µL (median count: 4500 cells/µL; case range: 1000 - 83,000 cells/µL; normal reference range: 150,000 - 450,000 cells/µL). Consistent with the signs of severe thrombocytopenia, twelve reports noted that the patient had mucosal bleeding (gingival, gastrointestinal, epistaxis), hemoptysis, petechiae, ecchymosis, or purpura. Most of these patients with thrombocytopenia recovered when quinine was discontinued and other therapeutic interventions were initiated. Thrombocytopenia is a labeled, well characterized, serious adverse event associated with quinine use.[7, 8]

The number of prescriptions in the United States for quinine far outpaces the number of opportunities to treat the disease for which it is indicated. These data suggest that the off-label use of quinine remains extensive.

FDA encourages Healthcare professionals to:

- Only prescribe quinine sulfate (Qualaquin) for the FDA-approved indication of treatment of uncomplicated *P. falciparum* malaria.
- Seek alternative therapies to treat nocturnal leg cramps or other musculoskeletal disorders, as quinine is not approved for these conditions. FDA

Table 1. Demographics

Age (years)		Gender	
Median	55.5	Male	14
Range	20-84	Female	22
Unknown	4	Unknown	2

Table 2. Indications and Outcomes

Reason for Use		Outcome*	
Leg Cramps	21	Hospitalization	17
Restless Leg Syndrome	4	Life-Threatening	11
Diarrhea Cramps	1	Death	5
Muscle Cramps	1	Other	5
Neuropathy	1		
P. Vivax Infection	1		
Unknown	9		

** Outcomes are not mutually exclusive*

RELEVANT WEBSITES

FDA Advances Effort Against Marketed Unapproved Drugs
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108799.htm

FDA Marketed Unapproved Drugs Website
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm

Federal Register Notices: (Access 1995 and 1998 quinine FR notices by the following page numbers: 19650 and 13526, respectively); *http://www.gpoaccess.gov/fr/retrieve.html*

REFERENCES

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2. Mali S, Steele S, Slutsker L, et al. Malaria Surveillance-United States, 2007. MMWR Surveill Summ 2009;58(SS-2):1-16.
3. Quinine sulfate (Qualaquin) product labeling. www.accessdata.fda.gov/drugsatfda_docs/label/2008/021799s008lbl.pdf
4. SDI: Vector One National (VONA) and Total Patient Tracker (TPT), 2006-2008, data extracted July and August 2008.
5. SDI: Physician Drug and Diagnosis Audit (PDDA), 2006-2008, data extracted July 2008.
6. Brinker A, Beitz J. Spontaneous reports of thrombocytopenia in association with quinine: clinical attributes and timing related to regulatory action. Am J Hemat. 2002;70:313-7.
7. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. NEJM. 2007;357(6):580-7.
8. Bougie DW, Birenbaum J, Rasmussen M, et al. Quinine-dependent, platelet- reactive monoclonals mimic antibodies found in patients with quinine-induced immune thrombocytopenia. Blood. 2009;113(5):1105-11.

ZOLEDRONIC ACID FOR OSTEOPOROSIS (MARKETED AS RECLAST)

Renal impairment and acute renal failure

Abstract: Reclast (zoledronic acid) is an FDA-approved bisphosphonate administered as a once-yearly intravenous infusion for the treatment of osteoporosis in postmenopausal women and men, Paget's disease of bone, and prevention and treatment of glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months. FDA's Adverse Event Reporting System (AERS) has received 24 cases of renal impairment and some cases of acute renal failure associated with the use of Reclast. As the label indicates, Reclast is not recommended for use in patients with severe renal impairment (creatinine clearance ≤ 35 mL/min). Physicians should monitor serum creatinine in patients with pre-existing renal compromise or other risk factors, including concomitant nephrotoxic medications or diuretic therapy, or severe dehydration, before and after each infusion. Based on new postmarket reports, the manufacturer has recently updated *Warnings and Precautions, Post-Marketing Experience,* and *Drug Interactions* sections of the Reclast label to include data on acute renal failure.

Keywords: Reclast, zoledronic acid, dehydration, acute renal failure

Zoledronic acid (marketed as Reclast and Zometa) is a bisphosphonate drug that works by inhibiting osteoclast-mediated bone resorption, slowing the breakdown of bone to help reduce the risk of fractures.[1] Reclast 5 mg was approved in 2007 as a once-yearly intravenous treatment for osteoporosis in postmenopausal women and for the treatment of Paget's disease of bone. In 2008, Reclast was approved for the treatment of osteoporosis in men and, in 2009, it was approved for the treatment and prevention of glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months. Zometa was FDA-approved in 2001 for the treatment of hypercalcemia of malignancy, multiple myeloma, and in conjunction with standard antineoplastic therapy in solid tumor patients with documented bone metastases.[2] Zometa is not discussed in this review given its different indication, patient population, and frequency of administration.

From April 2007 until February 17, 2009, FDA's Adverse Event Reporting System (AERS) received 24 evaluable postmarket cases of renal impairment and acute renal failure associated with the use of Reclast. Although some cases noted underlying medical conditions and/or concomitant medications, there were cases in which it was possible to establish a reasonable association between Reclast and the event.

Tables 1 and 2 list the characteristics of the 24 cases of renal impairment and acute renal failure after Reclast use. In this case series, osteoporosis was the most frequently cited reason for Reclast use. The median time-to-onset from the infusion until the event was 11 days.

Over half of the patients (14/24) had underlying medical conditions (e.g., diabetes mellitus, congestive heart failure, chronic kidney disease) that may have contributed to their risk of renal impairment or acute renal failure; or had concurrent exposure to known nephrotoxic medications (e.g., NSAIDs). Fifty-four percent of Reclast-associated acute renal impairment and failure cases (13/24) had documented transient increases in serum creatinine following drug infusion (median increase in serum creatinine was 4 mg/dL).

As noted in Table 2, many patients improved following intravenous fluid administration or other supportive care. Three patients required hemodialysis during their hospitalization. Seven deaths were reported. The cause of death was reported as acute renal failure in four patients. In these cases of death, however, there were other underlying medical conditions, concomitant medications, or a lack of information making any association between Reclast use and death due to acute renal failure difficult to establish.

Three representative cases associated with acute renal impairment and failure are described in Box 1. These cases were selected based on a close temporal relationship of acute renal failure to drug administration, and seriousness of the event. Of note, the patient in Case 2 was not a candidate for Reclast based on pre-infusion glomerular filtration rate (GFR) ≤ 35 mL/min, indicating pre-existing renal impairment.

The majority of the patients with renal impairment and acute renal failure associated with Reclast described in the AERS reports responded to hydration with intravenous fluids. In several cases, acute renal failure, dialysis, and death were reported in patients with pre-existing renal

Elements of a comprehensive treatment program for osteoporosis

Nutrition: Calcium and vitamin D are needed for strong bones

Exercise: Can improve bone health, increase muscle strength, coordination, and balance

Therapeutic Medications: There are several medication options available, including the use of bisphosphonates

http:www.niams.nih.gov/Health_Info/Bone/Osteoporosis/default.asp#a

Table 1. Demographics

Age (years)		Gender		Country of Origin	
Medium	75	Male	3	U.S.	22
Range	61-89	Female	19	Non-U.S.	2
Unknown	3	Unknown	2		

Table 2. Indications and Outcomes

Reason for Use		Outcome†	
Osteoporosis	20	Improvement with IV fluids	13
Paget's Disease	1	Hospitalization	18
Unknown	3	Required Dialysis	3
		Death‡	7

†Outcomes are not mutually exclusive. ‡Cause of death include renal failure (n=4), GI cancer (n=1), sepsis (n=1), and unknown causes (n=1).

BOX 1

Case 1

A 74-year old female with peripheral vascular disease including a history of aorto-iliac thrombosis, chronic diabetic renal disease, chronic obstructive pulmonary disease, and hypertension received Reclast 5 mg intravenously for the treatment of osteoporosis. She was previously treated with alendronate which was discontinued due to dyspepsia. Her baseline serum creatinine ranged from 1.3 to 1.6 mg/dL (normal reference range: <1.5 mg/dL) prior to her infusion. Seventeen days following the Reclast infusion, her serum creatinine level increased to 10.3 mg/dL. She experienced rapid deterioration of her renal function which led to her hospitalization. Her renal function did not improve with hemodialysis. The patient died, reportedly due to "complications from worsening of her other medical conditions." There were no concomitant medications listed in the report.

Case 2

An 83-year old female with chronic obstructive pulmonary disease, peripheral vascular disease, hypertension, and hyperlipidemia received Reclast 5 mg

Continued on page 15

BOX 1 (cont'd)

intravenously. Her concomitant medications included furosemide, atorvastatin, amlodipine, warfarin, diltiazem, pantoprazole, mirtazapine, Duonebs (albuterol/ipratropium), and pain medication. Her pre-infusion GFR was approximately 31 mL/min with an average serum creatinine of 1.4 mg/dL. Ten days after her Reclast infusion, she was admitted to the hospital with acute renal impairment (creatinine: 5.2 mg/dL). The reporter noted that that the patient took an unspecified diuretic and "may not have been hydrated enough." Dialysis was refused by the family. The patient died due to renal failure.

Case 3

An 84-year old female with atrial fibrillation, congestive heart failure, hypertension, chronic gastritis, hyperlipidemia and osteoporosis received Reclast 5 mg intravenously. Concomitant medications included lasix, zaroxlyn, warfarin, and digoxin. Her baseline serum creatinine was 1.1 mg/dL. She developed flu-like illness and was seen seven days after infusion. Other symptoms included constant nausea and occasional vomiting. She was admitted to hospital with dehydration and acute renal insufficiency (described as prerenal azotemia) with a blood urea nitrogen level of 64 mg/dL, creatinine of 4.1 mg/dL and digoxin level of 1.8 nmol/L. She received intravenous hydration and her creatinine improved to 1.5 mg/dL after three days. Her diuretic and digoxin medications were held until she was adequately hydrated. Symptoms improved, her dehydration resolved and she was subsequently discharged with a creatinine of 1.3 mg/dL.

insufficiency. These postmarket reports occurred in at-risk patients – those with underlying moderate to severe renal impairment or other risk factors including concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration.

Information outlined in the *Warnings and Precautions, Renal Impairment* section of the current label reports a transient increase in creatinine occurring within 10 days of dosing in 1.8% of Reclast-treated patients compared to 0.8% of placebo-treated patients. Based on postmarket reports, the manufacturer has recently updated *Warnings and Precautions, Post-Marketing Experience,* and *Drug Interactions* sections of the Reclast label to include data on acute renal failure.

Physicians are encouraged to:

- Avoid the use of Reclast in patients with severe renal impairment (creatinine clearance: < 35 mL/min).
- Monitor serum creatinine before each dose of Reclast.
- Consider interim monitoring of serum creatinine in at-risk patients; transient increases in serum creatinine may be greater in patients with impaired renal function.
- Assure that patients are adequately hydrated prior to administration of Reclast.
- Infuse Reclast over a period of at least 15 minutes.
- Report cases of renal impairment and acute renal failure in patients taking Reclast to FDA's MedWatch program at *www.fda.gov/medwatch.*

REFERENCES

1. Zoledronic acid (Reclast) Product Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021817s003lbl.pdf
2. Zoledronic acid (Zometa) Product Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21223lbl.pdf

REMINDER: HOW TO REPORT ADVERSE REACTIONS

Report serious adverse events to FDA's MedWatch reporting system by completing an online form at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178), by mail using the pre-paid postage address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

ARGININE HYDROCHLORIDE INJECTION (MARKETED AS R-GENE 10)

Fatal medication errors in a pediatric population

Abstract: A postmarket safety review of arginine hydrochloride (HCL) injection (R-Gene 10), a diagnostic drug used to evaluate pituitary function, identified several reports of medication errors and other adverse events associated with this drug. These reports from FDA's Adverse Events Reporting System (AERS) included four cases of fatal overdose in pediatric patients, instances of serious injection site and hypersensitivity reactions (labeled events), and several cases of hematuria (unlabeled events).

Keywords: arginine, medication errors, death, pediatrics

Since 1973, arginine HCL injection (marketed as R-Gene 10) has been an FDA-approved drug used to stimulate the pituitary gland in order to evaluate release of human growth hormone (HGH).[1] Arginine HCL is supplied in a 300 ml bottle of 10% arginine solution and contains 30 g of drug. The adult dose of arginine HCL is 30 g (1 bottle). The pediatric dose is 0.5 g/kg arginine HCL (5 ml of a 10% arginine solution per kg body weight). Arginine HCL injection should only be administered intravenously.

Arginine HCL injection can be used to aid in the diagnosis of:

Panhypopituitarism

Pituitary dwarfism

Chromophobe adenoma

Postsurgical craniopharyngioma

Hypophysectomy

Pituitary trauma

Acromegaly

Gigantism

Problems of growth and stature

In recent years, FDA has conducted two separate analyses of AERS related to arginine HCL injection. The first analysis addressed medication errors submitted to AERS from 1973 (time of marketing) to February, 2008. The second analysis addressed AERS reports of events that were not related to medication errors, again covering the period from 1973 through 2008.

FDA has received seven reports of medication errors associated with the use of arginine HCL injection. Most medication error cases resulted in an overdose of the drug in a pediatric patient (n = 6), including four with fatal outcomes (see Table 1). A case of arginine HCL overdose in children has also been described in the literature.[2] One case in this series involved the administration of arginine HCL injection by an improper route.

The ages of the children involved in the medication error case series ranged from 8 months to 3 years (one child's age was unknown). In cases of arginine HCL overdose, the dose of drug administered was reported to range from 3 to 10 times more than the indicated pediatric dose (0.5 g/kg). Box 1 details one case in which a child was given the wrong dose of arginine HCL.

Table 1. Outcomes Associated with Overdose of Arginine HCL Injection (n)

Vomiting (1)	Metabolic Acidosis (1)
Respiratory Distress (1)	Death (4)

BOX 1

In 2007, a 3-year old male child was prescribed an intravenous dose of 5.75 g arginine HCL to test for growth hormone deficiency. The pharmacy supplied two bottles of 10% arginine HCL solution to the clinic, each containing 300 ml of fluid (30 grams arginine/bottle). Although both bottles were labeled with the correct dose (5.75 g), the pharmacy hand wrote "1 of 2" on one bottle and "2 of 2" on the other bottle. For his infusion, the patient was given both bottles of arginine HCL intravenously for a total dose of 60 g of arginine HCL (a 10 fold overdose). During the infusion, the patient complained of a headache, stiffness and sleepiness, but the error in dosing was not recognized.[1] He was discharged from the clinic after the procedure.

At home, the patient had intractable vomiting, shakiness, weakness, and blue hands and lips. Approximately 10 to 12 hours post-arginine infusion, he was brought to the emergency room where he was found to be dehydrated and acidotic with his serum bicarbonate level 6 meq/L (reference: 24-30 meq/L). Upon hospital admission, the patient was lethargic,

Continued on page 17

BOX 1 (cont'd)

but arousable, and had periods of interaction with the healthcare team. Later that day, however, he developed extensor posturing. A CT-scan revealed cerebellar edema. He was transferred to the ICU with hypertension (systolic blood pressure 150 mm Hg) and bradycardia. His vital signs initially improved with intravenous administration of mannitol 0.5g/kg. However, his overall condition continued to deteriorate. Within hours, he developed abnormal breathing and seizure like activity. He became unresponsive and required intubation. Despite additional support with mannitol (5g/kg), 3% saline, and hyperventilation, he developed fixed and dilated pupils. Approximately 9 hours after ICU admission, the child was declared brain dead.

ARGININE HCL INJECTION-ASSOCIATED ADVERSE EVENT REPORTS

In addition to the reports of medication errors associated with arginine HCL, our second review of AERS identified 33 other adverse event reports associated with this drug. Although many of these events appear in the product label, some do not. In particular, this postmarket analysis identified several cases of hematuria in patients who had received an arginine HCL infusion.

Table 2 lists the selected demographics of these AERS cases. The majority of cases involved children (aged 16 years and younger) and used arginine HCL for diagnostic purposes. In one case, arginine HCL injection was used off-label to treat hyperammonemia. Table 3 lists reported adverse events associated with arginine HCL injection already included in the drug's label. Reported events not included in the label are also listed in Table 3. The most frequently reported labeled events were hypersensitivity (n=12) and injection site reaction (n=10). The most frequently reported unlabeled adverse event was hematuria (n=6).

Box 2 describes one case of hypersensitivity reaction, injection site reaction, and hematuria associated with the use of arginine HCL injection.

Table 2. Demographics (N=33)

Age		Gender	
Median	12 years	Male	20
Range	1-38 years	Female	9
<2 Years	2	Unknown	4
2 to 16 years	17		
≥ 17 years	6		
Unknown	8		

Table 3. Adverse Event*

Labeled	n	Non-Labeled	n
Hypersensitivity Reaction	12	Hematuria	6
Injection Site Reaction	10	Lethargy	2
Cerebral Edema	3	Perioral Tingling	2
Vomiting	3		
Headache	2		

*These events are not mutually exclusive

BOX 2

Hypersensitivity Reaction

A 34-year old female experienced an "anaphylactic reaction" within 15 minutes of starting arginine HCL injection. Her symptoms included perioral tingling and numbness, loss of consciousness, muscle twitching, and chest pressure. It was also noted that she was "unable to breathe." Her BP was 60/0 palpable. Her glucose level was 56 mg/dL. The infusion was stopped. She was given steroids, epinephrine, and diphenhydramine; and she was hospitalized for several days after the event. The patient's medical history included reactive hypoglycemia, chronic pain, hypotension, fibromyalgia, medication sensitivities, and head trauma.

Injection Site Reaction

A 17-year old male experienced an extravasation of fluid (leakage of fluid outside a vein) during an infusion of arginine HCL, resulting in a third-degree chemical burn. The patient was treated with Silvadene. At the time of the reporting, it was noted that the patient might require a skin graft.

Hematuria

Approximately 2 days after receiving an infusion of arginine HCL, a male child of unknown age experienced a "large amount of blood in his urine." The boy reported that he felt "razor blades upon urination." He also reported that he began experiencing urinary urgency and frequency. He was treated with antibiotics for presumed urinary tract infection. An ultrasound revealed that one kidney looked "larger and puffier than the other kidney, and there were blood clots in his bladder." Although the boy played football the day before the episode of hematuria, there was no mention of injury to the groin area.

Since marketing, a variety of adverse events have been reported to occur after the use of arginine HCL injection. Given that this drug is indicated as a stimulator of HGH from the pituitary, employed primarily for diagnostic purposes, it is commonly used in children. Healthcare professionals should always recheck their dosing calculations prior to administering arginine HCL injection. Healthcare professionals should also be aware that several unlabeled adverse events may be associated with the use of this drug. We continue to encourage healthcare professionals to report any suspected arginine HCL-associated adverse events to FDA's MedWatch program at *http://www.fda.gov/medwatch/*.

RELEVANT WEBSITES

Institute for Safe Medical Practices: *http://www.ismp.org/*

REFERENCES

1. R-Gene 10 Product labeling:*http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/16931slr028_r-gene_lbl.pdf*
2. Gerard JM, Luisiri A. A fatal overdose of arginine hydrochloride. J Toxicol Clin Toxicol. 1997;35(6):621-5.

ERRATUM: LENALIDOMIDE AND SERIOUS SKIN REACTIONS - DRUG SAFETY NEWSLETTER 2008; 1 (4); 43-6.

In the Summer 2008 issue of the Drug Safety Newsletter, we described a postmarket safety review of lenalidomide that identified cases of serious skin reactions, including reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme (pp. 43-6). Because the labeling for lenalidomide was recently changed, we are updating the recommendations provided in that article to clarify the severity of skin rash† that may warrant interruption or discontinuation of lenalidomide treatment (for recent revisions to lenalidomide product labeling, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021880s006s016s017lbl.pdf).

FDA encourages physicians to:

- Avoid lenalidomide therapy in patients with a prior history of Grade 4 rash (generalized exfoliative, ulcerative, or bullous dermatitis) associated with thalidomide treatment.
- Consider interrupting or discontinuing lenalidomide treatment if a patient develops a Grade 2 or 3 skin rash [macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA); severe, generalized erythroderma or macular, papular or vesicular eruption; or desquamation covering ≥50% BSA].
- Discontinue and not resume lenalidomide treatment if a patient develops angioedema, a Grade 4 skin rash, an exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected.

† Based on the Common Terminology Criteria for Adverse Events v3.0 (CTCAE; see *http://ctep.cancer.gov/reporting/ctc.html*).

DRUG SAFETY COMMUNICATIONS

Drug Safety Communications posted by FDA from December 1, 2008 to March 31, 2009 (advisories are available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm)

Date	Product(s)	Safety Issue
March 19, 2009	Insulin pens	Alert informing healthcare professionals about the risk of transmission of blood-borne pathogens from shared use of insulin pens. The insulin pens containing multiple doses are for use by a single patient only and should not be shared with another person.
March 5, 2009	Transdermal Drug Patches with Metallic Backings	Advisory highlighting the risk of skin burns during MRI scans from medicated transdermal patches with metallic backings.
February 23, 2009	Zonisamide (Zonegran and generics)	Alert informing healthcare professionals about the risk of metabolic acidosis in some patients following treatment with zonisamide.
February 19, 2009	Efalizumab (Raptiva)	Advisory highlighting reports of progressive multifocal leukoencephalopathy (PML) in patients taking efalizumab.
February 4, 2009	Xigris (drotrecogin alfa [activated])[1]	Ongoing safety review to further evaluate the increased risk of serious bleeding and deaths in patients with severe sepsis and baseline bleeding risk factors who receive Xigris.
January 26, 2009	Clopidogrel bisulfate (Plavix)[1]	Ongoing safety review to further evaluate the role of genetic factors and other drugs [especially the proton pump inhibitors (PPIs)] on the effectiveness of clopidogrel.
January 16, 2009	Topical anesthetics (prescription and over-the-counter)	Advisory highlighting information on potential hazards of skin products containing numbing ingredients for relieving pain from mammography and other medical tests and conditions.
January 13, 2009	Montelukast (Singulair)	Update of safety review finding that montelukast is not associated with suicide or suicidal behavior. FDA is continuing to review data to assess suicidal behavior, suicide, and other neuropsychiatric events (mood and behavioral adverse events) with other leukotriene receptor antagonists (zafirlukast and zileuton). At this time, FDA urges patients and prescribers to monitor for the possibility of neuropsychiatric events.
January 8, 2009	Ezetimibe/Simvastatin (Vytorin), Ezetimibe (Zetia), and Simvastatin (Zocor)	Update on data review evaluating the overall cardiovascular benefits of ezetimibe with simvastatin combination therapy. Overall, the cardiovascular benefit of combined ezetimibe and simvastatin does not appear to be significantly greater than simvastation alone, although some benefits were noted. Patients are encouraged to continue ezetimibe/simvastatin treatment unless otherwise directed by a healthcare professional.

Table continued from page 19

Date	Product(s)	Safety Issue
December 16, 2008	Antiepileptic drugs [carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol XR), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), valproate (Depakote, (Depakote ER, Depakene Depacon), zonisamide (Zonegran)]	Update highlighting a new labeled Warning and a Medication Guide about an increased risk of suicidal behavior, ideation and actions based on the FDA's pooled analysis of 199 clinical trials of eleven antiepileptic drugs.
December 11, 2008	Oral Sodium Phosphate Products (Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription)	Alert highlighting a new labeled Boxed Warning, a Medication Guide to reduce the risk of acute kidney injury, and FDA's request to conduct postmarket clinical trial to further assess the risk of acute kidney injury with use of these products.
December 2, 2008	Innohep (tinzaparin sodium injection)	Ongoing safety review to further evaluate an increase in all-cause mortality in patients who received the drug in the Innohep in Renal Insufficiency Study (IRIS). This multi-center European clinical trial was stopped due to this interim finding.

FOOTNOTES:

[1] Early Communication about an Ongoing Safety Review.

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