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

DRUG SAFETY NEWSLETTER

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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 every issue, the *Drug Safety Newsletter* provides information to health care professionals about product labeling changes, regulatory actions, and recent drug safety communications.

In this issue, we highlight two drug safety-related issues involving children. The first topic describes a risk associated with topical testosterone gel products. FDA has received postmarket reports of inappropriate development of early sex characteristics (i.e., enlargement of genitalia, advanced bone age, increased growth velocity, aggressive behavior) in children exposed to testosterone through contact with a person using these products. To mitigate this risk and increase awareness of this adverse event, FDA required a *Boxed Warning* on the product's prescribing information, as well as a Medication Guide.

The second topic describes reports of deaths of newborns and young infants associated with concomitant use of intravenous ceftriaxone (third-generation cephalosporin) and calcium-containing solutions. FDA has changed ceftriaxone's prescribing information based on these findings.

Our third topic is on reports of loss of sense of smell (anosmia) with Zicam zinc-containing intranasal products. These products were sold over-the-counter and used to reduce the duration and severity of cold symptoms. FDA has taken regulatory action to stop the marketing these products without FDA review and approval.

Beginning with this issue, we'll provide a brief quarterly update on drug safety topics discussed by FDA's Drug Safety Oversight Board (DSB).

We value your feedback. Please submit your comments to us at *http://www.accessdata.fda.gov/scripts/email/cder/comment.cfm*. We remind readers to report serious adverse events to FDA at *www.fda.gov/medwatch/report.htm*.

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Sr. Scientific Editor

POSTMARKET REVIEWS

TOPICAL TESTOSTERONE GEL PRODUCTS (MARKETED AS ANDROGEL 1% AND TESTIM 1%)

Secondary exposure of children to topical testosterone products

Abstract: Topical testosterone gels (marketed as AndroGel 1% and Testim 1%) are FDA-approved for use in men who either no longer produce testosterone or produce it in very low amounts. Since the initial marketing approval of testosterone gel in 2000 to May 2009, FDA's Adverse Event Reporting System (AERS) has received 20 pediatric postmarket reports of secondary exposure to topical testosterone gel (through contact with another person using testosterone gel drug products). Precautions in the current prescribing information instruct users to wash their hands after using the product and to cover the treated skin with clothing to minimize the potential for secondary exposure. The current prescribing information also states that children and women should avoid contact with testosterone application sites of men. Based on postmarket reports, FDA is requiring that manufacturers of two topical testosterone gel products, AndroGel and Testim, add a *Boxed Warning* to the prescribing information and develop safety strategies to protect children from secondary exposure.

Keywords: testosterone gel, secondary exposure, topical transfer

Topical testosterone gels (marketed as AndroGel 1% and Testim 1%) are FDA-approved for use in men who either no longer produce testosterone or produce it in very low amounts. Both products are applied once daily to intact skin of the shoulders or upper arms. AndroGel is also approved for application to the abdomen.[1,2] AndroGel and Testim were approved by FDA in February 2000 and October 2002, respectively.

Topical testosterone products represent approximately 65.6% of the total number of testosterone prescriptions dispensed between 2000 and November 2008. There were approximately 1.4 million prescriptions dispensed

for AndroGel and 400,000 prescriptions dispensed for Testim in 2008. The majority of prescriptions for AndroGel are dispensed to adult males 50-59 years of age. Pediatric patients (up to 17 years of age) account for less than 1% of prescriptions.[3,4]

Since the initial marketing approval of testosterone gel in 2000 to May 2009, FDA's Adverse Event Reporting System (AERS) received 20 reports (18 U.S. and 2 non-U.S.) describing adverse events in children who were exposed to testosterone gel that was used by another person (referred to as "secondary exposure"). The adverse events reported in these children included one or more of the following signs or symptoms: enlargement of the penis or clitoris, premature development of pubic hair, advanced bone age, increased self-stimulation, libido, erections, and aggressive behavior. An increased testosterone level was reported in more than half of these cases. The children ranged in age from 9 months to 7 years. Three of the 20 cases are described in the medical literature.[5,6,7]

In general, signs and symptoms improved and testosterone levels decreased when children were no longer exposed to the product. There were some reports that indicated the enlarged genitalia did not fully return to age-appropriate size, or the bone age remained modestly greater than the child's chronological age. Two children underwent clitoral reduction surgery.

Table 1 describes the characteristics of the cases. A representative case of secondary exposure to testosterone gel is described in Box 1. The case information was compiled from telephone interviews, laboratory reports, and written accounts from the child's mother and physician.

Table 1. Characteristics of U.S. (n=18) and non-U.S. (n=2) Pediatric Cases Associated with Reported Secondary Exposure to Testosterone Gel

Age		Gender	
Median	3 years	Male	9
Range	9 months to 7 years	Female	9
		Not reported	2
Products		**Adverse Events Reported More Than Once**	
AndroGel	15	Increased testosterone level	12
Testogel*	1	Enlarged genitalia	12
Testim	1	Pubic Hair	12
Testosterone gel Products (AndroGel and/or Testim)	3	Precocious puberty	6
		Aggression	5
		Bone age greater than chronological age	4
		Increased body hair	2
		Hypersexuality	2

*Testogel is not an approved drug product in the United States.

BOX 1

Case 1

A 3-year, 3-month old female was referred for an endocrine evaluation for the appearance of pubic hair. The family history was significant for the father applying three 5 g AndroGel packets per day (maximum FDA-approved dosage is two 5 g packet per day) since prior to the time of the child's birth. The report stated that the father washed his hands after applying AndroGel, covered the application site with clothing, and used a separate bathroom to shower.

On physical exam, the child had a height of 92.3 cm (15th percentile), weight of 14.1 kg (50th percentile), and BMI of 16.6 kg/m² (75th percentile). Her thyroid gland was normal to palpation. She had prepubertal breasts, pubic hair, no axillary hair, odor or freckling, as well as no acne or hyperpigmentation. She had an enlarged clitoris and posterior labial adhesions.

Laboratory results showed an elevated testosterone of 68 ng/dL (normal testosterone level for this child's age is less than 5 ng/dL) and no chromosomal abnormality. Adrenocorticotropic hormone stimulation test—performed to rule out congenital adrenal hyperplasia—was within normal limits. Pelvic and renal ultrasounds were unremarkable. The bone age was normal.

The pediatric endocrinologist advised the parents to make sure their daughter did not come in contact with the testosterone gel. Skin-to-skin contact was to be avoided, and the father was to be meticulous about washing his hands after applying AndroGel and covering the application site with a T-shirt.

In three weeks, the child's testosterone level decreased to 41 ng/dL. A month later, repeat labs showed testosterone level of 38 ng/dL. Due to the persistently elevated level, the endocrinologist recommended strict avoidance of any possible exposure to AndroGel. The father switched from the gel to testosterone injection. The family discarded bed linens and moved to a hotel for a month. The child's testosterone level decreased to normal levels (< 5 ng/dL).

In follow-up, the child, now 5 years of age, still has an enlarged clitoris for her age, but has normal testosterone levels, normal growth velocity, and no additional evidence of puberty.

Secondary exposure testosterone gel is a known, labeled adverse event. However, the mechanism of transfer is not clear. Approximately 10% of the testosterone dose applied on the skin is absorbed into the systemic circulation. Studies have indicated that a considerable amount of testosterone remains on the skin for a long period of time (> 8 hours) and is transferrable to others if the site of application is not washed.[8] Washing the application site, minimizes secondary exposure because it removes almost all the testosterone remaining on the skin. However, there are reports in AERS and published literature that suggest some secondary exposure to testosterone has occurred via shared washcloths or bed linens. These cases appear to have occurred despite adherence to precautions in the current prescribing information that instruct users to wash their hands after using the product and to cover the treated skin with clothing.

Testosterone gel is an androgen and medically indicated for replacement therapy in adult males with deficiency or absence of endogenous testosterone.[1,2]

Testosterone gel products are not FDA-approved for anti-aging, performance-enhancing, muscle building, or endurance purposes.

Testosterone is a Schedule III controlled substance, with abuse and misuse potential by athletes, bodybuilders, weight lifters, and young adults engaged in sports.

CURRENT STATUS

FDA is requiring the manufacturers of two prescription topical testosterone gel products (AndroGel 1% and Testim 1%) to include a *Boxed Warning* about the risk of secondary exposure. Precautions in the current prescribing information instruct users to wash their hands after use and to cover treated skin with clothing to minimize potential for secondary exposure. The prescribing information specifically instructs children and women (including pregnant women) to avoid contact with testosterone application sites on the skin of men who use these products.

The FDA recommends the following precautions be taken to minimize the potential for secondary exposure:

- Adults who use testosterone gels should wash their hands with soap and warm water after every application.
- Adults should cover the application site with clothing once the gel has dried.
- Adults should wash the application site thoroughly with soap and warm water prior to anticipated skin-to-skin contact with others.
- Adults should prevent children and women from coming into contact with testosterone application sites.
- Adults should note that use of any similar, but unapproved, products from the marketplace, including the Internet, can result in the same serious adverse effects and should be avoided.

The FDA is also requiring that the manufacturers of these products develop a Medication Guide as part of a Risk Evaluation and Mitigation Strategy (REMS) to minimize unintended secondary exposure to testosterone topical products and ensure that the benefits of these products continue to outweigh their potential risks. FDA

RELEVANT WEBSITES

FDA News: Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide: (5/7/2009) *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm*

FDA Briefing Information (including AndroGel) for the June 23, 2009 Meeting of the Pediatric Advisory Committee (PAC): *http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm166638.htm*

LETTERS FOR SAFETY LABELING CHANGES AND RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

AndroGel: *http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM161875.pdf*

Testim: *http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM161882.pdf*

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2. Testim product labeling: http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21454lbl.pdf.
3. IMS Health, IMS National Sales Perspectives, 2003-2008, data extracted Jan 2009.
4. SDI: Vector One: National (VONA) and Total Patient Tracker (TPT), 2000-2008, data extracted Jan 2009.
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INTRAVENOUS CEFTRIAXONE (MARKETED AS ROCEPHIN AND GENERICS) AND CALCIUM DRUG-DRUG INTERACTION:

Potential risk for cardiopulmonary adverse events in neonates

Abstract: FDA received seven case reports of serious cardiopulmonary adverse events in neonates associated with precipitation of a ceftriaxone-calcium salt in the lung and/or kidneys. Six neonates died. The children were aged 2 months and younger (range: 1 to 50 days), and treated with ceftriaxone for a variety of infections. The manufacturer and FDA issued a warning to healthcare professionals and revised the product labeling for the potential risk of concurrent administration of ceftriaxone and calcium. Ceftriaxone should not be used in neonates (≤ 28 days of age) if they are receiving or expecting to receive calcium-containing intravenous products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid. Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions in any age group.

Keywords: ceftriaxone, calcium, drug-drug interaction, cardiopulmonary arrest

Ceftriaxone was approved for marketing in the United States in 1984. This medicine is an injectable, 3rd generation cephalosporin with broad spectrum activity against gram-positive and gram-negative bacteria. Ceftriaxone's penetration into the central nervous system and long half life allows for once-daily dosing and has made it a valuable agent in the treatment of meningitis.

Since the approval of ceftriaxone, FDA's Adverse Event Reporting System (AERS) has received seven cases of serious cardiopulmonary adverse events in neonates associated with precipitation of a ceftriaxone-calcium salt in the lung and kidneys. All cases were from Europe. FDA has taken several regulatory actions to prevent the occurrence of similar cases in the United States.

FDA issued an alert to health care professionals in 2007, warning that ceftriaxone and calcium-containing products should not be administered within 48 hours of one another. FDA subsequently published more detailed information on the reported neonatal cases in the medical literature.[1]

In 2009, FDA updated recommendations based on additional in vitro data on the ceftriaxone/calcium interaction in adult and neonatal plasma, an ongoing analysis of reported cases, and a continuing safety review of data from FDA's AERS database. The manufacturer added new revisions to the *Warnings, Dosage and Administration, Contraindications, and Clinical Pharmacology* sections of the ceftriaxone's prescribing information.[2]

The current FDA recommendations on the concomitant use of ceftriaxone and calcium-containing intravenous solutions are:

- Do not reconstitute or mix ceftriaxone with a calcium-containing product, such as Ringer's or Hartmann's solution, or with parenteral nutrition containing calcium, because particulate formation can result.
- Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (≤ 28 days of age). Ceftriaxone should not be used in neonates (≤ 28 days of age) if they are receiving (or are expected to receive) calcium-containing intravenous products.
- In patients >28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group.

REPORTED CASES

From 1984 to January 2009, FDA received six reports of unanticipated deaths and one non-fatal case of a cardiopulmonary adverse event following concurrent therapy with intravenous ceftriaxone and intravenous calcium. Five of the seven patients were preterm infants.

The youngest infant was born at 30 weeks gestation. The ceftriaxone dose for six of the infants ranged from 80 to 200 mg/kg/day. One case was reported after one dose of ceftriaxone 50 mg/kg. Four of the infants received ceftriaxone doses ranging from 150-200 mg/kg per day (a dose greater than FDA's approved dosage of 50-100 mg/kg/day).

All patients received intravenous calcium. Six of the seven cases received calcium gluconate. One infant received calcium in hyperalimentation. Information about underlying disease, drug dosage and infusion times, as well as other concurrent therapies was often incomplete in the reports. Six neonates died. Five patients had a post-mortem examination. The autopsy findings from four of the five infants documented the presence of "crystalline" material or white precipitate in the lungs, kidneys, heart, and/or liver. No analysis of the crystalline material was performed in any of these cases.

At least four infants had received multiple doses of ceftriaxone. One infant received 5 days of therapy at the time of death. In this case, the nurse noticed a white precipitate in the infant's IV tubing 2 hours following intravenous ceftriaxone, approximately 30 minutes after intravenous calcium gluconate, and during intravenous amikacin administration. The nurse cleared the tubing by "pushing" the precipitate into the infant. Following this action, the child went in to cardiopulmonary arrest. A white precipitate was noted in the pulmonary artery during the autopsy. In this case, no analysis of the precipitate was performed.

Three representative cases of this adverse event are described in Box 1. All three infants received concomitant intravenous calcium and ceftriaxone therapy. One infant had a positive rechallenge. A repeat cardiopulmonary event occurred after the second dose. In two cases, the white crystalline precipitate was found in the intravascular bed during autopsy, suggesting the formation of a ceftriaxone-calcium salt.

Ceftriaxone is an injectable, 3rd generation cephalosporin with activity against gram-positive and gram-negative bacteria.

Ceftriaxone penetrates the central nervous system and is used in the treatment of meningitis.

The long half-life of this drug allows for once daily dosing.

The safety and effectiveness of ceftriaxone in neonates, infants, and pediatric patients have been established.

The seriousness of these events, coupled with their preventable nature, has led the FDA and the manufacturer to issue an important warning to the medical community regarding the potential risk of concurrent administration of ceftriaxone and calcium.

There are no data on interactions between intravenous ceftriaxone and oral calcium-containing products, or between intramuscular ceftriaxone and intravenous or oral calcium-containing products. Healthcare professionals should report patients who have adverse events following ceftriaxone administration to the FDA's MedWatch program (*www.fda.gov/medwatch/report.htm*).

BOX 1

Case 1

A premature male infant—gestational age 30 weeks—presented at 50 days of age with a *Klebsiella pneumoniae* urinary tract infection. He received gentamicin, ceftriaxone (50 mg/kg over 2 minute IV push), as well as calcium-containing hyperalimentation. The infant developed shock with bradycardia, pallor, and apnea 10 minutes after ceftriaxone injection. He was successfully resuscitated. A similar event occurred 10 minutes after a second dose given on the following day (rechallenge). The reporter could not rule out anaphylactoid reaction (the mother received ceftriaxone during pregnancy) or ceftriaxone and calcium salts precipitate from hyperalimentation solution as potential causes of the event.

Case 2

A 3-week old infant, receiving ceftriaxone for fever of unknown origin, died after 3 weeks of treatment. The infant was receiving ceftriaxone concurrently with calcium gluconate intravenously. An autopsy revealed cardiomyopathy and the presence of crystals in the lungs.

Case 3

An infant—gestational age 35 weeks—was treated with ceftriaxone 200 mg IV every 24 hours for maternal amnionitis. The patient also received calcium gluconate 10% infusion via the intravenous Y-site and a white precipitate was noted at the end of the IV tubing. The infant developed pulmonary embolism and died approximately 2 hours after ceftriaxone administration. A white precipitate was noted on autopsy.

RELEVANT WEBSITE

Information for Healthcare Professionals: Ceftriaxone: *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109103.htm*

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1. Bradley JS, Wassel RT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. Pediatrics. 2009;123(4):e609-13.
2. Ceftriaxone (Rocephin) product labeling: *http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/0550585s063lbl.pdf*

ZINC-CONTAINING INTRANASAL COLD PRODUCTS (MARKETED AS ZICAM) AND ANOSMIA

Abstract: FDA alerted consumers that Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs, Kids Size (a discontinued product) have been associated with long-lasting or permanent anosmia (a loss of the sense of smell). These zinc-containing intranasal products were marketed as cold remedies used to reduce the duration and the severity of cold symptoms. However, these products have not been shown to be effective for such use. Since the initial marketing of Zicam products in 1999 until June 2008, FDA has received more than 131 reports of anosmia associated with use of Zicam zinc-containing intranasal products. All reports were from the United States. In June 2009, FDA issued a warning to the manufacturer to remove these products from the market based on evidence supporting a causal association between intranasal zinc and anosmia. Consumers are warned to stop using the Zicam nasal products immediately.

Keywords: Zicam, zinc-containing intranasal cold remedies, anosmia, ageusia, loss of sense smell, loss of sense of taste

On June 16, 2009, FDA alerted healthcare professionals and consumers that Zicam Cold Remedy Nasal Gel (Zincum Gluconicum), Zicam Cold Remedy Nasal Swabs (Zincum Gluconicum), and Zicam Cold Remedy Swabs, Kids Size (Zincum Gluconicum) have been associated with long lasting or permanent anosmia (loss of the sense of smell). These products were available without a prescription, marketed as homeopathic remedies, and contained zinc gluconate as their active ingredient. The products were widely marketed for use in adults and children to reduce the duration and the severity of cold symptoms. However, these products have not been shown to be effective in the reduction of the duration and severity of cold symptoms. These products were widely marketed. Two-thirds of all Zicam intranasal products sold are the zinc-containing Cold Remedy products.[1] This safety information does not concern oral zinc tablets and lozenges taken by mouth.

In recent years, there is a growing body of evidence from nonclinical, clinical, and adverse event report data supporting a causal association between anosmia and zinc-containing nasal cold remedies. On June 16, 2009, FDA issued a warning letter to stop marketing Zicam intranasal zinc gluconate products.

From initial marketing of Zicam products in 1999 to June 18, 2008, FDA's Adverse Event Reporting System (AERS) received 131 reports of individuals who developed anosmia associated with the use of intranasal zinc-containing Zicam products. All of the reports were from the United States. The reports indicate that Zicam was used for the prevention of the common cold and to treat cold symptoms, usually for a relatively short period of time (median duration of use was 3 days). The individuals ranged from 23 to 82 years old with a median age of 48 years. The most frequently reported additional symptoms included burning and pain in the nose, as well as headaches.

In most cases (127 of the 131 reports), anosmia following the use of Zicam intranasal products was persistent and still ongoing at the time the report was submitted (see Table 1).

Table 1. Duration of anosmia associated with the use of intranasal zinc-containing Zicam products in AERS reports.†

Total number of reports	131
Persistent anosmia at time of report	127 (97%)
Range	2 days-4 years
# of Reports where anosmia lasted ≥ 6 months	38
Mean Duration	7 months
Median Duration	3 months

†Duration of anosmia was determined by the difference in time between the date of onset of anosmia and the date FDA received the report, unless the AERS report indicated a specific duration in the case narrative.

The abrupt onset of the anosmia, clinical presentation (severe burning or pain), and persistent (unresolved at time of report) loss of smell are inconsistent with post-viral anosmia and support an association between the intranasal Zicam products and developing anosmia. The onset and duration of anosmia in these reports are also consistent with cases of anosmia associated with the use of Zicam reported in the medical literature.[2,3]

Two representative cases of intranasal Zicam-associated with anosmia are described in Box 1.

Zicam Cold Remedy Nasal Gel, Zicam Cold Remedy Nasal Swabs, and Zicam Cold Remedy Swabs, Kids Size were marketed without review and approval through FDA's new drug application (NDA) process. Based on the cumulative data discussed briefly in this article, FDA warned the manufacturer to stop marketing zinc intranasal products without FDA approval. Through the NDA process, the manufacturer must provide information to demonstrate that the products are safe and effective.

Healthcare professionals are encouraged to remind consumers that:

- They should stop using these products and throw them away.
- They should contact their healthcare professional if they experience loss of smell or taste, or experience other problems after using any zinc-containing nasal products.
- There are a number of other over-the-counter drugs for treating symptoms of the common cold that they can take. However, the common cold goes away without treatment, usually within 7 to 10 days.
- They should report serious adverse events or product quality problems associated with the use of these products to the FDA's MedWatch Adverse Event Reporting Program at *www.fda.gov/medwatch*. FDA

RELEVANT WEBSITE

Public Health Advisory on Zicam Intranasal Zinc Products: *http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm166059.htm*

Warning Letter: *http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm166909.htm*

Zicam Fact Sheet: *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm166927.htm*

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BOX 1

Case 1

A 35-year old male developed nasal burning, pain, and loss of sense of smell following use of Zicam brand "no drip nasal gel", active ingredient Zincum Glurconicum 2x. These symptoms occurred within one hour of product use. The patient immediately flushed the nasal passages with saline solution to reduce the pain. Approximately 5 hours following initial use, he experienced intense pain in the region of his sinuses and a migraine-like headache extending from his head to his neck. He repeated saline rinses of the nasal passages and noticed that he couldn't smell anything—even roasted coffee beans in a jar had no scent. He was admitted to the emergency room, and his sinuses were noted to be red and inflamed during the exam. He was referred to an ear, nose, and throat (ENT) specialist. The following few days, he continued to experience burning and sinus pain. The patient still had a very dull sense of smell and was unable to smell coffee at the time of this report. No further information is available.

Case 2

A 42-year old woman used two squirts of Zicam Cold Remedy Nasal Gel at bedtime to treat nasal congestion due to crying. She did not have a cold. She had immediate burning of the nose and could not smell or taste the next day. She saw an ENT specialist who performed a rhinoscopy and diagnosed the patient as having anosmia. At the time of the report, approximately two months after the event, she described her sense of smell as being almost non-existent and her taste was distorted, and in some cases, non-existent.

FDA'S DRUG SAFETY OVERSIGHT BOARD

FDA's Drug Safety Oversight Board (DSB) was formed in 2005 to provide advice to the CDER Center Director on managing and communicating emerging drug safety issues. The DSB also provides a forum for discussion and arbitration of internal debates concerning the management of potential drug safety issues. The DSB does not provide clinical recommendations or advice to healthcare professionals or the public. The Board meets monthly and is composed of representatives throughout FDA and our other federal partners, such as the National Institutes of Health, Department of Veterans Affairs, Centers for Disease Control and Prevention, Department of Defense, and Agency for Healthcare Research and Quality. Although meetings are internal, a summary of each meeting is posted on FDA's website.

Drug Safety Oversight Board Meeting Summary

May 21, 2009: The DSB discussed the role of meta-analyses in FDA's reviews of drug safety. The Board specifically addressed meta-analysis performed by academia and other health care organizations where the results identified a new drug safety issue not addressed in the full prescribing information for the drug product. The Board discussed how FDA should best understand and incorporate the abundance of research publications using meta-analyses into its decision-making processes involving drugs.
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm168786.htm

June 18, 2009: The DSB discussed reports of metabolic acidosis, metabolic acidosis with increased anion gap, and neuropsychiatric adverse events in children using polyethylene glycol (PEG) products. Neuropsychiatric adverse events include seizures, tremors, tics, headache, anxiety, lethargy, sedation, aggression, rages, obsessive-compulsive behaviors including repetitive chewing and sucking, paranoia and mood swings. The Board discussed whether the adverse event reports could constitute a safety signal for use of PEG products in children and what action, if any, might be appropriate for the prescription and over-the-counter preparations.
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm171059.htm

July 16, 2009: The DSB heard presentations on the following topics:

1. The Freedom of Information Act and how it applies to the DSB.
2. The Veterans Health Administration and FDA collaboration on the propoxyphene issues.
3. Goals and scope of FDA's Safe Use Initiative: The Board discussed what types of Safe Use projects would be of interest, how Safe Use could define project priorities and boundaries, and what can be used as measures of success.
4. A Follow-up on 21 Early Communications about an Ongoing Safety Review (ECs) issued from August 2007 to July 2009: Elements of an EC were given along with a brief description of each EC, the projected date for follow-up, actual date of follow-up, and the follow-up actions.

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm176355.htm

DRUG SAFETY COMMUNICATIONS

Drug Safety Communications posted by FDA from April 1, 2009 to July 1, 2009
(http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm)

Date	Product(s)	Safety Issue and Web Address
July 1, 2009	Varenicline (Chantix) and bupropion (Zyban, Wellbutrin, and generics)	Alert informing healthcare professionals about a new labeled *Boxed Warnings* and patient Medication Guides highlighting the risk of serious neuropsychiatric symptoms in patients with use of these products. *http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm169988.htm*
July 1, 2009	Insulin glargine (Lantus)[1]	Ongoing safety review to assess an increased risk for cancer in patients with diabetes mellitus. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169722.htm*

DRUG SAFETY COMMUNICATIONS *Table continued from page 28*

Drug Safety Communications posted by FDA from April 1, 2009 to July 1, 2009
(http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm)

Date	Product(s)	Safety Issue and Web Address
June 17, 2009	Cefepime (Maxipime)	Update highlighting information about FDA's meta-analysis to reevaluate mortality. FDA concluded that the increase in mortality in cefepime-treated patients was not statistically significant compared to comparator-treated patients. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm167254.htm*
June 16, 2009	Zicam zinc-containing intranasal products	Advisory highlighting the risk of long lasting or permanent loss of sense of smell (anosmia). FDA recommends that consumers stop using these products or dispose them. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm166834.htm*
June 15, 2009	Focalin, Focalin XR (dexmethylphenidate HCl); Dexedrine, Dexedrine Spansules, Dextroamphetamine ER, Dextrostat (dextroamphetamine sulfate); Vyvanse (lisdexamfetamine dimesylate); Desoxyn (methamphetamine); Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin-LA, Ritalin-SR (methylphenidate); Adderall, Adderall XR (mixed salts amphetamine); Cylert (pemoline) and generics	Ongoing safety review to evaluate the risk of sudden death with use of stimulant medications to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165858.htm*
June 12, 2009	Montelukast (Singulair), Zafirlukast (Accolate), and Zileuton (Zyflo and Zyflo CR)	Ongoing safety review of clinical trial data to evaluate mood and behavioral-related adverse events. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm*
June 11, 2009	Sirolimus (Rapamune)	Alert informing healthcare professionals of clinical trial data that suggest increased mortality in stable liver transplant patients after conversion from a calcineurin inhibitor (CNI)-based immunosuppressive regimen to sirolimus. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165015.htm*
June 3, 2009	Propylthiouracil	Alert highlighting the risk of serious liver injury, including liver failure and death in adult and pediatric patients. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm162701.htm*

DRUG SAFETY COMMUNICATIONS *Table continued from page 29*

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Date	Product(s)	Safety Issue and Web Address
May 1, 2009	Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B)	Update highlighting FDA's request from the manufacturers to strengthen Warnings in product labeling and add a Boxed Warning, regarding the serious risk regarding distant spread of toxin. In addition, the manufacturers are required to develop and implement a Risk Evaluation and Mitigation Strategy (REMS), including Medication Guide to assure safe use. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm143819.htm*
April 21, 2009	Ceftriaxone (Rocephin)	Update highlighting important revisions to product labeling about the interaction of ceftriaxone with calcium-containing products and new recommendations for neonates (≤28 days of age) and for patients >28 days of age. *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109103.htm*

FOOTNOTES:

[1] Early Communication about an Ongoing Safety Review.

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