Drug Safety Revisions: FDA Update

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Atorvastatin (Lipitor®)
Manufacturer: Pfizer, Inc.
Indication: This medication is an adjunct to diet and exercise to reduce elevated total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB), and triglyceride (TG) concentrations and to increase high-density lipoprotein-cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia.

Rationale for FDA Alert: Albers Medical Distributors, Inc., has voluntarily recalled three lots of 90-count Lipitor® 10 mg, National Drug Code 0071-0155-23. Med-Pro, Inc., of Lexington, Nebraska, repackaged the product, and the labels say “Repackaged by Med-Pro, Inc., Lexington, NE” in the lower left-hand corner. The following lot numbers were affected:

- 20722V: 90-tablet bottles; expiration date 9/04
- 04132V: 90-tablet bottles; expiration date 01/04
- 16942V: 90-tablet bottles; expiration date 09/04

The Food and Drug Administration (FDA) has indicated that these products are or might be counterfeit and that their distribution should be stopped. This recall extends to the consumer level. The FDA has urged both health care providers and patients to check the packaging carefully before using this product. Patients who have this product, with any of these three lot numbers, should not ingest it and should return it to their pharmacies.

On June 17, 2003, the FDA expanded its recall of certain Lipitor® products and all Lipitor® products repackaged by Med-Pro (with the designation number 68850) and distributed by Albers in Kansas City, Missouri, and H.D. Smith Wholesale Drug Company in Springfield, Illinois.

Conclusion: In conjunction with the FDA, Albers expanded the original voluntary recall to include all of the atorvastatin lots that it had purchased that were packaged by Med-Pro, Inc. Although the FDA has not tested all of the additional lots, Albers is voluntarily recalling them as a precautionary measure.

Risperidone (Risperdal®)
Manufacturer: Janssen Pharmaceutica
Indication: Risperidone is indicated for the treatment of schizophrenia.

Rationale for Labeling Review: In four placebo-controlled trials involving elderly patients with dementia-related psychosis (n = 1,230), the incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, was significantly higher in patients taking risperidone than in patients taking placebo.

Label Change Warning: Cardiovascular Adverse Events, including Stroke, in Elderly Patients with Dementia. Cardiovascular adverse events, including fatalities, were reported in placebo-controlled trials of risperidone in elderly patients (mean age, 85 years; range, 73–97) with dementia-related psychosis. The incidence of cerebrovascular adverse events in the patients taking risperidone was significantly higher than in those taking placebo. Risperidone has not been shown to be safe or effective in the treatment of these patients.

Conclusion: In the spring of 2003, a new paragraph was added to the package insert for risperidone concerning an increased frequency of cerebrovascular adverse events in clinical trials of elderly patients with dementia-related psychosis who took risperidone for two years compared with the frequency in patients taking placebo. Mortality rates for cerebrovascular adverse events were comparable between the two treatment groups. Based on a decision by the FDA, the label change is limited to geriatric patients with dementia; according to the manufacturer, however, risperidone is not indicated for the treatment of dementia, as is true for other antipsychotic drugs.

Gynecare Intergel Adhesion Prevention Solution®
Manufacturer: Gynecare Worldwide, a division of Ethicon, Inc.
Indication: The solution is intended for use in “open” conservative gynecological procedures as an adjunct to good surgical technique to reduce postsurgical adhesions. Adhesions are abnormal bands of scar tissue that connect organs or tissues that should be separate. Once adhesions develop, the only way to remove them is by another surgical procedure called adhesiolyis.

Rationale for Market Withdrawal: The manufacturer is conducting a voluntary withdrawal of the solution to assess information obtained during postmarketing experiences with the solution, including adverse events associated with its off-label use in laparoscopy and in nonconservative surgical procedures such as hysterectomy.

Postmarketing reports include late-onset postoperative pain and repeated surgeries following the onset of pain, noninfectious foreign-body reactions, and tissue adhesions. In some patients, a residual material was observed during subsequent surgery. Postoperative pain can suggest other serious complications, and physicians should be aware of this when managing patients after surgery.

Conclusion: As many as 90% of women undergoing gynecological surgery experience adhesions or internal scarring, a postsurgical complication that can cause chronic pelvic pain, infertility, and small-bowel obstruction.

The solution was approved to reduce the likelihood of moderate or severe postoperative adhesions and is indicated for use in some traditional open laparotomy procedures. The manufacturer is conducting a voluntary withdrawal of the solution to assess information obtained during postmarketing experiences with the solution, including adverse events associated with its off-label use in laparoscopy and in nonconservative surgical procedures such as hysterectomy.

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facturer plans to conduct a thorough evaluation of the technical issues, surgical techniques, and circumstances associated with the adverse postmarketing events.

**Gamma-Hexachlorocyclohexane Lindane Lotion or Shampoo USP, 1% (Kwell®)**

**Manufacturer:** Alpharma and Morton Grove Pharmaceuticals  

**Indications:** Lindane (gamma-hexachlorocyclohexane; formerly gamma benzene hexachloride) is approved for the topical treatment of pediculosis and scabies in patients who either have not responded to adequate doses or are intolerant of other approved therapies. Lindane has been on the market since 1951 but was labeled as a second-line therapy in 1995 because safer alternative treatments are available that should be used first. With a second-line treatment, either of the following conditions is true:

- The patient cannot tolerate the first-line drug of choice.  
- The patient has used the first-line drug of choice as instructed, and the treatment has not succeeded.

Other medications have also been approved to treat human infestations, for example:

**For scabies:**  
- permethrin cream 5% (Acticin™, Bertek; Elimite®, Allergan; Nix® Cream)

**For lice:**  
- crotamiton cream 10% (Eurax®, Novartis Consumer)  
- malathion lotion 0.5% (Ovide® Lotion, Medicis)  
- pyrethrum 0.33%/piperonyl butoxide 4% shampoo and cream rinse (e.g., A-200®, Hogil; RID®, Bayer Consumer)  
- permethrin 1% (Nix® Lice Treatment Creme Rinse)

**Rationale for Labeling Revision:** The FDA's voluntary Adverse Event Reporting System (AERS) indicates that the serious events reported have been attributed to misuse of lindane products; 17 deaths have been associated with lindane use and three of these have been confirmed as a result of lindane.

Neurological side effects, ranging from dizziness to seizures, have been reported. Newborns, children, people weighing less than 110 pounds (50 kg), and older patients are at greatest risk for neurological effects.

**Label Change, Boxed Warning:** Lindane shampoo should be used only in patients who cannot tolerate or who have not responded to first-line treatment with safer medications for the treatment of scabies and lice.

**Neurological Toxicity:** Seizures and deaths have been reported following the use of lindane shampoo with repeated or prolonged application and, in rare cases, even after a single application according to directions. As mentioned previously, the shampoo should be used with caution in infants, children, the elderly, individuals with other skin conditions, and people who weigh less than 110 pounds.

**Contraindications:** Lindane shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.

**Proper Use:** Patients must be instructed on the proper use of the shampoo (e.g., the amount to apply and how long to leave it on) and on ways to avoid the need for re-treatment. Patients should know that itching occurs after the successful killing of lice and is not necessarily an indication for re-treatment with the shampoo.

**Conclusion:** The FDA has determined that lindane products have benefits that outweigh risks when they are used as directed. Most of the serious adverse events reported in association with lindane products have been a result of misuse, although serious reactions have occurred with apparently normal use. These reports highlight the need to emphasize the potential toxicity of lindane in the product labels; to educate health care providers and patients about the risks and how to minimize them; and to develop mechanisms to facilitate safe use after the drug is dispensed to patients. These mechanisms include:

- having lindane products available only in small packaged amounts to avoid excess applications.  
- requiring that pharmacists give the medication guide to all patients with each new prescription.

The adverse events of concern with lindane are systemic and are a result of absorption of this lipophilic drug following its topical application. Most of the serious effects have occurred in patients with contraindications to its use, in patients who used the medication in excessive amounts, or in patients who misused the product. Most commonly, patients reapply lindane because of continued itching after the treatment, either by their own volition or upon their doctor's recommendation. Because most of the serious adverse effects of lindane products have been caused by misuse and overuse, especially with the lotion, package sizes are being limited to one and two ounces.