

CDC to Monitor Seasonal Flu Vaccine for Seizures

BY SHARON WORCESTER

FROM A MEETING OF THE CDC'S
ADVISORY COMMITTEE
ON IMMUNIZATION PRACTICES

ATLANTA – Reports of febrile seizures in young children in Australia and New Zealand following vaccination with a 2010-2011 seasonal trivalent influenza vaccine have the Centers for Disease Control and Prevention watching closely

for signs of trouble in the United States.

The CDC will collaborate closely with international scientists, partners, and regulatory authorities, and will collaborate on animal pyrogenicity studies using the vaccine in question, Dr. Michael McNeil reported at the meeting.

Furthermore, existing vaccine safety data systems currently in place for the 2009 H1N1 monovalent vaccine – which is included in the 2010-2011 seasonal

vaccine, will be used to monitor for seizures and febrile seizures following vaccination with the seasonal vaccine. These systems, including the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), are capable of detecting signals for seizure risk early in the course of the vaccination season, said Dr. McNeil of the CDC's immunization safety office.

The reports of seizures in Australia

earlier this year led the chief medical officer there to suspend use of the 2010-2011 seasonal trivalent influenza vaccine for all children younger than 5 years. Prior to that suspension, the recommendation for all of Australia was that seasonal vaccination be administered to children with chronic medical conditions who were aged 6 months to 18 years. In Western Australia, vaccination was recommended for all children aged 6 months to 5 years.

The predominant vaccine used in Australia was trivalent Fluvax Junior, manufactured by the Australia-based biopharmaceutical company CSL Ltd., which dominates the market there; CSL vaccine accounted for nearly all trivalent seasonal vaccine distributed there by late April. A preliminary investigation revealed a signal suggesting an increase in febrile seizures, mostly among children younger than 5 years in the 24 hours following vaccination, with an estimate of up to 9 cases per 1,000 vaccinated, compared with an estimate of fewer than 1 case per 1,000

The reports of seizures in Australia earlier this year led to the suspension there of the 2010-2011 seasonal trivalent influenza vaccine in all children younger than 5 years.

vaccinated with the 2009 H1N1 monovalent vaccine alone, Dr. McNeil reported.

To date, no biologic, clinical, or epidemiologic factors have been identified to explain the increase in febrile seizures following vaccination, and no abnormalities have been detected in the vaccine, he said.

Although New Zealand has suspended use of the CSL vaccine following the four reports of febrile seizures after vaccination with that product there, other countries in the Southern hemisphere that have childhood vaccination programs, including Argentina, Chile, and South Africa, have not reported febrile seizures, and the World Health Organization has received no reports of febrile seizures associated with other 2010-2011 seasonal influenza vaccines, including Vaxigrip (Sanofi-Aventis) and Influvac (Solvay Pharmaceuticals Inc.).

Dr. McNeil noted that CSL vaccines have been used for those aged 18 years and older in the United States since 2007, and that a CSL vaccine was licensed for children aged 6 months and older in November 2009, although very few doses of that trivalent seasonal vaccine were distributed in the 2009-2010 influenza season.

VAERS data showed no cases of febrile seizures following administration of CSL's seasonal vaccine for children aged 6 months and older, and only four cases following administration of the CSL 2009 H1N1 monovalent vaccine, all of which occurred in adults. No signal was detected by VAERS or VSD for seizure following any 2009-2010 seasonal influenza vaccines or H1N1 vaccines, he said.

BRIEF SUMMARY

ALTABAX® (retapamulin ointment), 1%

The following is a brief summary only; see full prescribing information for complete product information.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Irritation

In the event of sensitization or severe local irritation from ALTABAX, usage should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted [see Patient Counseling Information (17)].

5.2 Not for Systemic or Mucosal Use

ALTABAX is not intended for ingestion or for oral, intranasal, ophthalmic, or intravaginal use. ALTABAX has not been evaluated for use on mucosal surfaces [See Patient Counseling Information (17)]. Epistaxis has been reported with the use of ALTABAX on nasal mucosa.

5.3 Potential for Microbial Overgrowth

The use of antibiotics may promote the selection of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. Prescribing ALTABAX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The safety profile of ALTABAX was assessed in 2,115 adult and pediatric patients ≥9 months who used at least one dose from a 5-day, twice a day regimen of retapamulin ointment. Control groups included 819 adult and pediatric patients who used at least one dose of the active control (oral cephalixin), 172 patients who used an active topical comparator (not available in the US), and 71 patients who used placebo.

Adverse events rated by investigators as drug-related occurred in 5.5% (116/2,115) of patients treated with retapamulin ointment, 6.6% (54/819) of patients receiving cephalixin, and 2.8% (2/71) of patients receiving placebo. The most common drug-related adverse events (≥1% of patients) were application site irritation (1.4%) in the retapamulin group, diarrhea (1.7%) in the cephalixin group, and application site pruritus (1.4%) and application site paresthesia (1.4%) in the placebo group.

Because clinical studies are conducted under varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Adults: The adverse events, regardless of attribution, reported in at least 1% of adults (18 years of age and older) who received ALTABAX are listed in Table 1.

Table 1. Adverse Events Reported by ≥1% of Adult Patients Treated With ALTABAX in Phase 3 Clinical Studies

Adverse Event	ALTABAX N = 1527 %	Cephalixin N = 698 %
Headache	2.0	2.0
Application site irritation	1.6	<1.0
Diarrhea	1.4	2.3
Nausea	1.2	1.9
Nasopharyngitis	1.2	<1.0
Creatinine phosphokinase increased	<1.0	1.0

Pediatrics: The adverse events, regardless of attribution, reported in at least 1% of pediatric patients aged 9 months to 17 years who received ALTABAX are listed in Table 2.

Table 2. Adverse Events Reported by ≥1% in Pediatric Patients Aged 9 Months to 17 Years Treated With ALTABAX in Phase 3 Clinical Studies

Adverse Event	ALTABAX N = 588 %	Cephalixin N = 121 %	Placebo N = 64 %
Application site pruritus	1.9	0	0
Diarrhea	1.7	5.0	0
Nasopharyngitis	1.5	1.7	0
Pruritus	1.5	1.0	1.6
Eczema	1.0	0	0
Headache	1.2	1.7	0
Pyrexia	1.2	<1.0	1.6

Other Adverse Events: Application site pain, erythema, and contact dermatitis were reported in less than 1% of patients in clinical studies.

7 DRUG INTERACTIONS

Co-administration of oral ketoconazole 200 mg twice daily increased retapamulin geometric mean AUC₍₀₋₂₄₎ and C_{max} by 81% after topical application of retapamulin ointment, 1% on the abraded skin of healthy adult males. Due to low systemic exposure to retapamulin following topical application in patients, dosage

adjustments for retapamulin are unnecessary when co-administered with CYP3A4 inhibitors, such as ketoconazole. Based on in vitro P450 inhibition studies and the low systemic exposure observed following topical application of ALTABAX, retapamulin is unlikely to affect the metabolism of other P450 substrates.

The effect of concurrent application of ALTABAX and other topical products to the same area of skin has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Effects on embryo-fetal development were assessed in pregnant rats given 50, 150, or 450 mg/kg/day by oral gavage on days 6 to 17 postcoitus. Maternal toxicity (decreased body weight gain and food consumption) and developmental toxicity (decreased fetal body weight and delayed skeletal ossification) were evident at doses ≥150 mg/kg/day. There were no treatment-related malformations observed in fetal rats.

Retapamulin was given as a continuous intravenous infusion to pregnant rabbits at dosages of 2.4, 7.2, or 24 mg/kg/day from day 7 to 19 of gestation. Maternal toxicity (decreased body weight gain, food consumption, and abortions) was demonstrated at dosages ≥7.2 mg/kg/day (8-fold the estimated maximum achievable human exposure, based on AUC, at 7.2 mg/kg/day). There was no treatment-related effect on embryo-fetal development.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALTABAX should be used in pregnancy only when the potential benefits outweigh the potential risk.

8.3 Nursing Mothers

It is not known whether retapamulin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALTABAX is administered to a nursing woman. The safe use of retapamulin during breast-feeding has not been established.

8.4 Pediatric Use

The safety and effectiveness of ALTABAX in the treatment of impetigo have been established in pediatric patients 9 months to 17 years of age. Use of ALTABAX in pediatric patients is supported by evidence from adequate and well-controlled studies of ALTABAX in which 588 pediatric patients received at least one dose of retapamulin ointment, 1% [see Adverse Reactions (6), Clinical Studies (14)]. The magnitude of efficacy and the safety profile of ALTABAX in pediatric patients 9 months and older were similar to those in adults.

The safety and effectiveness of ALTABAX in pediatric patients younger than 9 months of age have not been established.

8.5 Geriatric Use

Of the total number of patients in the adequate and well-controlled studies of ALTABAX, 234 patients were 65 years of age and older, of whom 114 patients were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients.

10 OVERDOSAGE

Overdosage with ALTABAX has not been reported. Any signs or symptoms of overdose, either topically or by accidental ingestion, should be treated symptomatically consistent with good clinical practice.

There is no known antidote for overdoses of ALTABAX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with retapamulin.

Retapamulin showed no genotoxicity when evaluated in vitro for gene mutation and/or chromosomal effects in the mouse lymphoma cell assay, in cultured human peripheral blood lymphocytes, or when evaluated in vivo in a rat micronucleus test.

No evidence of impaired fertility was found in male or female rats given retapamulin 50, 150, or 450 mg/kg/day orally.

17 PATIENT COUNSELING INFORMATION

Patients using ALTABAX and/or their guardians should receive the following information and instructions:

- Use ALTABAX as directed by the healthcare practitioner. As with any topical medication, patients and caregivers should wash their hands after application if the hands are not the area for treatment.
- ALTABAX is for external use only. Do not swallow ALTABAX or use it in the eyes, on the mouth or lips, inside the nose, or inside the female genital area.
- The treated area may be covered by a sterile bandage or gauze dressing, if desired. This may also be helpful for infants and young children who accidentally touch or lick the lesion site. A bandage will protect the treated area and avoid accidental transfer of ointment to the eyes or other areas.
- Use the medication for the full time recommended by the healthcare practitioner, even though symptoms may have improved.
- Notify the healthcare practitioner if there is no improvement in symptoms within 3 to 4 days after starting use of ALTABAX.
- ALTABAX may cause reactions at the site of application of the ointment. Inform the healthcare practitioner if the area of application worsens in irritation, redness, itching, burning, swelling, blistering, or oozing.

ALTABAX is a trademark of GlaxoSmithKline.

Revised: June 2010

ALX:3BRS

©2010, GlaxoSmithKline. All rights reserved.



GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709