DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: September 5, 2006

PID # D060652

TO: Renata Albrecht, M.D., Director
Division of Special Pathogens and Transplant Products (DSPTP)

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)

FROM: Andrew D. Mosholder, M.D., M.P.H., Medical Officer, DDRE

PRODUCT: Gemifloxacin (Factive®) NDA 21-158 (Sponsor: Oscient)

SUBJECT: Update to July 26, 2006 Memorandum on Cutaneous Reactions Associated With the Use of Gemifloxacin

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Verispan approves this clearance request in full. 9/6/06

1. EXECUTIVE SUMMARY

The purpose of this memorandum is to update the July 26, 2006 DDRE memorandum on gemifloxacin cutaneous reactions with additional analyses of postmarketing reports. An Adverse Event Reporting System (AERS) database search was conducted 8-2-2006 for serious cutaneous reactions reported in the U.S. that involved serious outcomes for gemifloxacin and a comparator oral antibiotic (cefditoren) used for the treatment of similar respiratory tract infections. These case reports were individually reviewed with a

particular search for events which might fall in the category of severe cutaneous adverse drug reactions. In addition, recent Periodic Safety Update Reports for gemifloxacin were reviewed to account for cases too recent to have been entered into the AERS database. Estimates of the population use of these antibiotics were obtained from Verispan, L.L.C. and included the Vector One™: Total Patient Tracker (TPT) and Vector One®: Physician Drug and Diagnosis Audit (PDDA). A total of 24 serious skin reactions for gemifloxacin were found, including three possible cases of Stevens-Johnson syndrome (SJS); unfortunately, critical clinical details that might have ruled SJS in or out were not provided. Other gemifloxacin serious skin reactions included 7 reports of serious allergic reactions. An upper estimate of patients exposed to gemifloxacin in the U.S. is approximately 1.2 million; estimation is made difficult by the large amount of patient samples which are not captured in prescription data. Given the short duration of exposure with a typical course of treatment of gemifloxacin, and the relative rarity of SJS in the general population, even a single case of SJS would not be expected among U.S. patients receiving gemifloxacin. Finally, serious cutaneous adverse events were reported more frequently for gemifloxacin than for the comparator antibiotic cefditoren, after adjustment for level of use, but such comparisons must be viewed very cautiously. Continued postmarketing surveillance of cutaneous adverse events with gemifloxacin is recommended, to include vigorous follow-up of initial reports and expedited reporting to FDA of all serious cutaneous adverse events, regardless of whether the particular event is considered unlabeled or labeled.

This analysis of individually reviewed serious skin reactions is consistent with the findings of our initial post-marketing drug risk assessment[1] of gemifloxacin cutaneous reactions and both of these reviews expand upon the clinical picture of gemifloxacin cutaneous toxicity that was shown in gemifloxacin clinical trials. The currently available post-marketing data do not give us assurance that our concerns regarding cutaneous toxicity of gemifloxacin should be any less serious when larger patient populations are exposed. The magnitude of the benefit gained from the use of gemifloxacin for the indication under discussion (Acute Bacterial Sinusitis) need to be clearly defined to weigh the magnitude of this drug-related risk associated with gemifloxacin.

2. BACKGROUND

Please refer to the DDRE Memorandum dated July 26, 2006 on cutaneous reactions associated with the use of gemifloxacin.[2] To follow-up that analysis of postmarketing data for gemifloxacin cutaneous adverse events, an adjudicated review of reported serious skin reactions for gemifloxacin and a comparator antibiotic, cefditoren was proposed. The purpose of this memorandum is to provide that additional adjudicated review and comparison.

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[1] Farinas ER, Truffa M, Ahmad SR, Brinker A. Memorandum: Cutaneous Reactions Associated With the Use of Gemifloxacin. July 26, 2006.

[2] Farinas ER, Truffa M, Ahmad SR, Brinker A. Memorandum: Cutaneous Reactions Associated With the Use of Gemifloxacin. July 26, 2006.

When considering the postmarketing data for gemifloxacin and skin reactions, it is important to remember that an association with rash was observed in gemifloxacin clinical trials. As described in the Factive labeling,[3] rash occurred with an overall risk of 2.8% of patients exposed in the clinical trial program, and was more frequent among females, among patients below the age of 40, and with longer duration of treatment. Seven gemifloxacin-treated patients in clinical trials had rashes that were considered serious adverse events.[4] In four cases the patients were hospitalized. The age range for these cases was 18-72; four of the seven patients were female. One rash was diagnosed as serum sickness, but no specific dermatological diagnoses were reported for the other cases. These seven serious rash adverse events out of a total of 8,119 patients exposed in clinical trials yields a risk of serious rash events of approximately 1 in 1200 exposures.

3. METHODOLOGY

A. AERS Searches

On August 2, 2006, the Adverse Event Reporting System (AERS) database was searched[5] for cases meeting the following criteria:

Suspect Drug: gemifloxacin, cefditoren
U.S. location
Skin and subcutaneous tissue disorders System Organ Class (SOC)
Serious outcome[6]
Time frame: from launch through 8-2-06

In addition, foreign AERS reports for gemifloxacin were reviewed, and the last four Periodic Safety Update Reports (PSURs) submitted by Oscient were manually reviewed for reports of serious cutaneous adverse events too recent to have been entered into the AERS database. Also, narratives of non-skin serious AERS cases for gemifloxacin were reviewed to screen for any cases which should have been reported under the skin SOC.

B. Individual review of cases

Particular emphasis was placed on reports that might represent one of the cutaneous adverse drug reactions known to be associated with morbidity or mortality (such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypersensitivity syndrome, angioedema, anaphylaxis, serum sickness, or cutaneous vasculitis).[7] Cases in which the reporter had designated the outcome as "serious" but which upon review did

[3] Available at www.factive.com
[4] Oscient Pharmaceuticals Corporation. Factive (gemifloxacin) Tablets for the treatment of acute bacterial sinusitis briefing document. August 7, 2006.
[5] Thanks to Dr. Allen Brinker, DDRE, for performing the AERS search
[6] On the MedWatch form, serious cases are those designated by the reporter as fatal, life-threatening, involving hospitalization, causing disability, involving a congenital anomaly, requiring intervention to prevent permanent impairment, and "other."
[7] Wolf R, Orion E, Marcos B, Matz H. Life-threatening acute adverse cutaneous drug reactions. Clinics in Dermatology 2005;23:171-181.

not require hospitalization or emergency medical care, and did not appear to represent one of the aforementioned severe cutaneous adverse drug reactions, were excluded. Examples of cases excluded in this manner would be reports in which the reporter checked the "Other" box for serious outcome, with comments limited to "medically significant," "severe rash," etc., and no further description. In addition, reports of skin adverse events which did not appear relevant to the assessment of adverse cutaneous drug reactions were excluded (e.g., petechiae with thrombocytopenia), as were rashes that were not serious in themselves but occurred in the clinical setting of a non-skin serious event.

A special search for cases of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) was performed. The case definition for SJS employed was that of La Grenade et al.[8] Briefly stated, these authors considered a postmarketing case report of SJS to be definitive if it was reported with a confirmed diagnosis and/or if the description included blistering over 10% of the body surface with mucous membrane involvement. A second category of possible cases were those lacking definitive information but described as possible SJS.

C. Drug use data

1. Sponsor estimate

Please refer to Oscient's Briefing Document[9] for details on how the sponsor estimated the number of patients treated with gemifloxacin since marketing.

2. Verispan, LLC data sources

Patient exposure data were available from Verispan, LLC's Vector One®: Total Patient Tracker (TPT), and Vector One®: Physician Drug and Diagnosis Audit (PDDA). The TPT involves nationally projected estimates of unique patients from Verispan's Vector One® data warehouse which contains over 2 billion prescriptions per year filled by over 160 million patients in the outpatient retail pharmacy setting. The PDDA is a database derived from a monthly survey of approximately 3,100 office based prescribers and includes demographic and diagnostic information on patients prescribed specific drugs. This survey captures drug mentions or occurrences, which may or may not be equivalent to a prescription. In some cases, a drug may be mentioned in connection with more than one diagnosis in the same patient, resulting in double counting. The PDDA survey data are also projected nationally, although the level of imprecision in these projections is somewhat higher because of a smaller sample size. PDDA captures samples of drug products given to patients without a prescription, which prescription-based audits such as

[8] La Grenade L, Lee L, Weaver J, Bonnel R, Karwoski C, Governale L, Brinker A. Comparison of reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. Drug Safety 2005;28:917-924.

[9] Oscient Pharmaceuticals Corporation. Factive (gemifloxacin) Tablets for the treatment of acute bacterial sinusitis briefing document. August 7, 2006.

TPT do not. On the other hand, it is conceivable that patients may not fill all the prescriptions reported by physicians participating in the PDDA survey.

4. RESULTS

A. Drug Use Information

The following table displays the drug use data obtained from Verispan, LLC and the sponsor.

Table 1. Estimates of U.S. patient exposures to selected antibiotics

Drug	Approval date	2002-Jun 2006 Verispan TPT pt. count[10]	Verispan PDDA occurrences 2002-Jun 2006[11]	Sponsor patient exposure estimate[12]
Gemifloxacin (Factive)	Apr 2003*	332,114	1,183,000	760,000
Cefditoren (Spectracef)	Aug2001**	512,156	1,412,000	-

*Launched in 2004 **No significant use until 2002

Note that the sponsor's gemifloxacin use estimate falls between the TPT and PDDA estimates.

B. AERS data for gemifloxacin on serious cutaneous reactions

1. Domestic AERS data

Appendix Table 1 displays the AERS reports from the U.S. of serious cutaneous reactions with gemifloxacin. There were no definitive cases of SJS reported, and no TEN cases reported. There were 3 possible SJS cases in AERS for which the clinical information was lacking to make a definitive classification. (There was an anonymous report of a fourth possible SJS case, but this information was impossible to confirm or further evaluate.)

Six reports described serious cutaneous reactions of an allergic nature; two of these involved anaphylaxis-like events. An additional twelve reports described other serious cutaneous events that did not appear to be either allergic in nature, or to represent possible SJS, although in several reports critical clinical details were missing that might have permitted a more definitive classification.

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[10] Source data: Verispan Total Patient Tracker, Year 2002 - June 2006 Aggregate Time, Extracted 8-23-06;TPT Mosholder A060251 8-23-06 FacSpecKet aggregate (2).xls

[11] Source data: Verispan, Physician Drug and Diagnosis Audit (PDDA), Years 2004 - June 2006, Extracted 8-23-06; PDDA Mosholder A060251 8-23-06 FacSpecKet Occurrances lg 8-29-06.xls; PDDA Mosholder A060251 8-23-06 Spectracef RPOccurrances (2).xls

[12] Oscient Pharmaceuticals Corporation. Factive (gemifloxacin) Tablets for the treatment of acute bacterial sinusitis briefing document. August 7, 2006.

2. Foreign AERS data

There have been only 3 AERS reports of any kind received from other countries for gemifloxacin; all 3 are from South Africa, and all 3 describe apparent allergic reactions. One involved a severe allergic reaction, including bronchospasm, but no cutaneous manifestations; the other two involved serious allergic reactions with urticaria.

B. Domestic AERS data on cefditoren for serious cutaneous reactions

There were three AERS reports of serious cutaneous reactions with cefditoren, as shown in Appendix Table 2. Of these, two involved apparent anaphylaxis, and one was a case of serum sickness.

The following table summarizes the numbers of reports for the drugs of interest.

Table 2. Counts of U.S. serious cutaneous adverse event reports for selected antibiotics

Drug	2002-6/2006 TPT total patients	PDDA occurrences 2002-6/2006	Numbers of reports			
			Definite SJS	Possible SJS	Serious allergic skin	All serious skin
Gemifloxacin	332,114	1,183,000	0	3	9	24
Cefditoren	512,156	1,412,000	0	0	3	3

5. EPIDEMIOLOGICAL ANALYSES

There is considerable range to the estimates of patient exposures to these drugs. Sampling appears to account for a large proportion of the use of these drugs, which is plausible because an entire course of treatment may only require 5 or 10 pills. Because TPT does not take into account sampling, it is likely to provide underestimates of the numbers of patients treated. The PDDA, for reasons explained above, can overestimate numbers of patients, but because it does attempt to account for sampling, it will be used in the calculations to follow.

A. Reporting rates

To calculate reporting rates for serious cutaneous adverse events, the 8/2/2006 AERS search was used to provide the numerator, in order to provide a comparison between drugs; cases found with the individual review of PSURs and non-skin serious reports were excluded from the numerator. The PDDA estimates of occurrences for each drug provided the denominator. In this manner, the following reporting rates were obtained.

Table 3. AERS reporting rates for U.S. cases of serious cutaneous events/million PDDA occurrences

Drug	Possible SJS	Definite SJS	Serious allergic skin	All serious skin
Gemifloxacin	2.5	0	3.4	11.0
Cefditoren	0	0	2.1	2.1

B. Person time estimate

To determine a meaningful population exposure time in patient-years it is necessary to attribute a duration of time for each patient treated in the data displayed above. Courses of treatment with gemifloxacin are typically 5 or 7 days, and with cefditoren, 10-14 days. Review of the time to onset for the reports of cutaneous events shows that some did not develop until several days after treatment was discontinued. Accordingly, to estimate the person time at risk for serious cutaneous events associated with treatment, a window of two weeks following the longest labeled duration of treatment will be assumed. Thus, the window for gemifloxacin will be 21 days per use, and for cefditoren, 28 days. Taking the PDDA occurrences for each drug and allocating these windows of person time at risk for cutaneous reactions yields the following exposure estimates in patient years: gemifloxacin, 68,000 patient years; cefditoren, 108,000 patient years. If a briefer duration of time at risk per course of treatment is assumed, these estimates will shrink accordingly.

6. Discussion and Recommendations

In the postmarketing environment, gemifloxacin has been associated with serious skin reactions, including serious allergic reactions and other reactions requiring hospital treatment. Some reported cases may have been SJS but crucial clinical details were lacking.

Although it was originally proposed to compare spontaneous reporting data for gemifloxacin to that for telithromycin and cefditoren, the comparison to telithromycin postmarketing surveillance data proved problematic, because of the high profile postmarketing safety issues surrounding that antibiotic with respect to liver toxicity, as well as its much greater level of use. Accordingly, only the comparison to cefditoren, for which the level of utilization is similar to gemifloxacin, is presented herein. When use in the population is accounted for, serious cutaneous adverse events with gemifloxacin were reported at a higher rate than for cefditoren. However, such comparisons should be viewed cautiously and may be of limited inferential value, because of uncertainties regarding both the numerator (due to under-reporting and difficulty classifying cases) and the denominator (due to difficulties estimating the population use of the drugs).

These data are subject to the well-known limitations of spontaneous report data, which include uncertainty regarding drug causality of the event, under-reporting of events, biases operating to make reporting more or less likely, and quality of the information

reported.[13] For the assessment of rare adverse drug events with a broad differential diagnosis, attributes which apply to life-threatening cutaneous adverse drug reactions, the twin problems of under-reporting and limited clinical details for the cases that are reported are significant limitations. With respect to under-reporting of serious skin drug reactions, there are data from a Canadian study about the degree of under-reporting for TEN.[14] The authors surveyed records from hospital burn units for a five year period and ascertained the number of patients admitted for a diagnosis of TEN. During the same five year study period, 25 cases of TEN were reported to the Canadian postmarketing surveillance system, but there were 250 cases of TEN admitted to Canadian burn units, suggesting that only some 10% of TEN cases requiring burn unit treatment had been reported.

Cases of SJS and TEN are relatively rare in the general population. Estimates of the population incidence of SJS have ranged from 1 to 6 per million per year;[15] a 1981-85 survey of medical centers in West Germany yielded a population incidence rate of 1 per million per year for SJS, and 0.9 per million per year for TEN.[16] As calculated above, the relevant person-time of exposure in the U.S. to gemifloxacin is probably well under 100,000 person-years. The estimated person-time exposures are relevant to the question of how many cases of SJS or TEN might be expected to occur in the absence of a causal relationship to drug treatment. If one assumes a background incidence rate of 1-6 per million per year for SJS, then there would be less than one case of SJS expected among patients exposed to gemifloxacin in the U.S. At this point in time, therefore, even a single well-documented case of SJS might suggest a causal relationship to gemifloxacin. It bears emphasis that several cases described herein may well have been SJS, but the clinical information required to make such a determination was not obtained.

As described in the labeling for cefditoren[17], extensive foreign postmarketing experience with this antibiotic (first marketed in Japan in 1994) has shown it to be associated with erythema multiforme, SJS and TEN. However, these events were not represented in the AERS search for serious cutaneous reactions reported in the U.S., where there were only 3 serious skin reactions, all 3 of an allergic nature. This further illustrates that the limited U.S. exposure for cefditoren has not been sufficient to detect SJS or TEN as has been observed in foreign postmarketing data. Thus, the absence of SJS or TEN reports with gemifloxacin in the U.S. should not be regarded as reassuring, given that the postmarketing exposure in the U.S. for gemifloxacin is comparable to that of cefditoren.

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[13] Goldman SA, Kennedy DL, Graham DJ, et al. The clinical impact of adverse event reporting. CDER Staff College, October 1996.

[14] Mittmann N, Knowles SR, Gomez M, Fish JS, Cartotto R, Shear NH. Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. Drug Saf. 2004;27(7):477-87.

[15] Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995;333:1600-7.

[16] Schopf E, Stuhmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: An epidemiologic study from West Germany. Arch Dermatol 1991;127:839-842.

[17] Available at www.spectracef.com

This analysis of individually reviewed serious skin reactions is consistent with the findings of our initial post-marketing drug risk assessment of gemifloxacin cutaneous reactions and both of these reviews expand upon the clinical picture of gemifloxacin cutaneous toxicity that was shown in gemifloxacin clinical trials. The currently available post-marketing data do not give us assurance that our concerns regarding cutaneous toxicity of gemifloxacin should be any less serious when larger patient populations are exposed.

Recommendations: (1) Continued postmarketing surveillance of cutaneous adverse events with gemifloxacin, including vigorous follow-up of reports of serious cutaneous reactions. (2) All serious cutaneous adverse events + severe cutaneous adverse events of interest (i.e., SJS, TEN, Erythema Multiforme) for gemifloxacin should receive expedited reporting, even if the event is considered labeled/listed. (3) The magnitude of the benefit gained from the use of gemifloxacin for the indication under discussion (Acute Bacterial Sinusitis) needs to be clearly defined to weigh the magnitude of this drug-related risk associated with gemifloxacin.

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Appendix Table 1. U.S. postmarketing serious cutaneous adverse events reported with gemifloxacin (*=found in screening of Periodic Safety Update Report and non-skin serious AERS reports case, all other cases obtained from AERS search of skin SOC)

Mfr ID	Source	Indication	Age Sex	Onset	Descripton	Concomitant illness	Concomitant medication	Outcome, Comments
Possible Stevens Johnson Syndrome (SJS) cases								
2005US FACT00 342	MD via sales rep	Respiratory tract	> 40	?	Severe rash, "not maculaopaular, not benign, and like SJS"	?	?	Hospitalized, treated with epinephrine and other drugs. Further details including outcome unknown
FACT06 00069	Pt family member	"Strep throat"	18 F	Itching after 1 dose	Itching treated with diphenhydarmine, then "hives," "discolored skin, blisters in her mouth and vaginal blisters" and "SJS."	None NKA	None	Hospitalized 7 days and treated with steroids. Attempts to obtain additional information unsuccessful
2004US FACT00 083	MD, RN via sales rep	Sinus	67 F	Day 3 or 4	Diffuse maculopapular rash with mucosal and vaginal lesions. ER physician diagnosis = SJS.	?	? Treated initially with Levaquin	Hospitalized for 2-3 days and received IV steroids. No additional information obtained. Spnosor's consultant dermatologist opinion: not SJS
--	Anonymo us	?	?	?	"bordered on Steven's Johnson syndrome" [sic]	?	?	Author of anonymous note. [redacted] report rashes, including this possible SJS case.
Other rashes with serious outcomes								
FACT 0500009	MD via sales rep	Respiratory tract	20s F	Day 6 (1 day after d/c)	Hospitalized for "rash"	?	?	Treatment and outcome information not obtained
FACT06 00206	MD via sales rep	Pneumonia	80 F	Day 9 (2 days after d/c)	Diffuse red, itchy, maculopapular rash, fever; diagnosed as "drug induced allergic rash." No mucous membrane involvement; liver enzymes WNL.	Allergic to sulfonamide, PCN, Viactiv	Synthroid 100 mcg/d; hydrocodone	Hospitalized and improved with prednisone and IV fluids.
FACT05 00684	MD via sales rep	Pnuemonitis	17 F	Day 7	Diffuse, itchy, macular "fire engine red" rash. Also developed swollen knees.	Recent mononucleosis	Allegra	Hospitalized by dermatologist and treated with prednisone. Rash and knee swelling resolved. Dermatologist was not reporter. No additional follow-up information.
FACT05 00420	Spouse	Pnuemonia	37 F	Approx. day 5	Sunburn like, itchy rash, over 85% of body; hospitalized and treated with steroids	Allergic to sulfa	none	No follow up information obtained; at time of report pt. had been hospitalized for 3 days but was improving.
FACT05 00549	MD via sales rep	Bronchopne umonia	47 F	Day 2	Diffuse, erythematous rash, pain and swelling esp. of the face. Fever, desquamation. Skin biopsy: perivascular interstitial dermatitis with eosinophils c/w drug eruption.	Diabetes mellitus type II	Diovan HCT, Lasix 20 mg prm, KCl, Dynacirc CR 10 mg	Hospitalized and improved with steroid therapy; diagnosis drug reaction with eosinophilic dermatitis
FACT05 00386	Consumer , MD	Respiratory/ bronchial	66 F	Day 6	Hives, headaches, shaking, itching, tongue felt "sunburned." Hives lasted for weeks; photosensitivity; considered disabling	Atrial fib., hypertension, asthma, drug allergies	Warfarin, amiodarone, Cardizem, clonidine, albuterol inhaler	Hives persisted despite treatment with steroid. Patient died several months later during oral surgery procedure.
FACT06 00107*	MD via sales rep	Respiratory	55 F	Day 9 (4 days post d/c)	Hospitalized for severe, itchy red rash on entire body and inside mouth	Herpes zoster	Hormone replacement, med for H. zoster	No further details, outcome unknown

Mfr ID	Source	Indication	Age Sex	Onset	Descripton	Concomitant illness	Concomitant medication	Outcome, Comments
FACT06 00182*	MD via sales rep	Cellulitis	31 F	-	Fever and erythematous, lacy rash began with Bactrim, worsened after gemifloxacin	Liver disase, cellulitis	Bactrim prior	Hospitalized for fever and worsening rash, which was attributed to sulfa. Recovered.
FACT06 00238*	MD via sales rep	CAP	21 M	?	Maculopapular, mild, diffuse, itchy, may have been hospitalized			Recovered, possibly after treatment with Medrol and Benadryl
FACT06 00239*	MD via sales rep	CAP	40 F	?	Maculopapular, mild, diffuse, itchy, may have been hospitalized			Recovered, possibly after treatment with Medrol and Benadryl. Same reporter as previously listed case.
FACT06 00272*	MD via sales rep	?	? F	?	Rash requiring hospitalization for 5-7 days	?	None	No further details
FACT06 00222*	RN via sales rep	Sinusitis, bronchitis	37 M	Day 6 (1 day post d/c)	Morbiliform rash, including palms and soles, fever, pustulosis on scalp, sore throat, periorbital swelling, possible blistering on soft palate but no other mucosal involvement. Dx dermatitis medicamentosus	Allergic rhinitis, GERD	Nexium, steroids	Hospitalized and treated with Atarax with improvement
Cutaneous manifestations of serious allergic reactions								
FACT05 00675	MD via sales rep	Sinusitis, bronchitis	32 F	Day 8 (1 day after d/c)	Maculopapular rash, cough, dyspnea, pharyngeal edema; admitted for treatment of "angioedematous reaction"	Asthma; tongue swelling with Amoxil	None	Treated with steroids and antihistamine and recovered, but skin reported to be peeling and weeping after discharge
FACT05 00728	MD	Bronchitis	20 F	1 hr after first dose	Rash (not further described) and anaphylaxis, ER visit	-	None	Treated with epinephrine, Benadryl, Medrol
FACT05 00667	Consumer who is MD	Sinusitis	44 M	Day 6 (1 day after d/c)	Anaphylactic event with shortness of breath, trouble swallowing, confusion, progressive macular rash	NKA Used Levaquin with no problems	-	Hospitalized and received IV steroid, antihistamine; rash had not resolved at discharge
2006PV0 12252	Consumer	UTI	56 F	?	Severe rash legs, stomach, chest; diagnosed in ER as allergic vasculitis	Diabetes type 2; Allergic to PCN, Zetia, Lipitor	Byetta 5 mcg BID	Treated with "steroid pack." Later had similar reaction to Macrobid
FACT06 00108*		Acute Bronchitis	55 M	30 min post first dose (Factive and Lodrane 12 D)	Tongue swollen, face swollen, red, and itchy, difficulty swallowing, eyes red	NKA	Lodrane 12-D	Received emergency treatment at office of prescriber
FACT06 00130*	MD via sales rep	Bronchitis	42 F	Day 7	Urticaria,lip swelling	Allergic rhinitis, use of Levaquin with no problems. Allergy to PCN	Steroids, Flonase, Zyrtec, Advair	Admitted for "urticaria, allergic drug reaction" Treated successfully with steroids and antihistamine
FACT05 00419*	MD	Sinusitis	40M	1 dose	Anaphylaxis with difficulty breathing, rash/hives, facial and oral swelling	NKA	Allegra	Treated successfully in ER with epinephrine
FACT06 00043*	Consumer	Respiratory	49 F	1/2 hour after 1st dose	Cough, shortness of breath, eyes swelling, hives, light headed	Latex allergy		Treated in ER for acute allergic reaction with epinephrine, IV Benadryl, prednisone

Mfr ID	Source	Indication	Age Sex	Onset	Descripton	Concomitant illness	Concomitant medication	Outcome, Comments
FACT06 00081*	Consumer , MD, RN	Otitis media	?F	Day 8	Diffuse rash, difficulty swallowing, wheezing, swelling of mouth and throat, dx "anaphylactic reaction"	NKA	?	Required hospital intensive care treatment, recovered

Appendix Table 2. U.S. serious cutaneous adverse events reported with cefditoren

Mfr ID	Source	Indication	Age Sex	Onset	Descripton	Concomitant illness	Concomitant medication	Outcome, Comments
USA20040 013924	MD via sales rep	Sinusitis	14 F	Day 22 (12 days post d/c)	Serum sickness with polyarthritis, urticaria	None, NKA	Flonase	Responded to prednisone and antihistamine. Designated serious for "medically significant"
USA20040 018045	MD	Otitis media	55 M	Day 2	Anaphylaxis with hives, difficulty breathing	GERD, DJD of knees	Nexium, Darvocet-N, Zantac	Treated initially in ER then had to return for hospital admission; recovered
USA20040 014050	MD via sales rep	?	79 F	?	Anaphylaxis and angioedema	Pulmonary disease	?	Hospitalized and recovered after treatment with antihistamine

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MEDICAL OFFICER

Gerald DalPan
9/6/2006 03:53:02 PM
MEDICAL OFFICER