Subject: 1013-74

This 67-year-old White female subject weighing 70.3 kg received azithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Azithromycin (500 mg daily) was administered orally from 03 February 2000 until 05 February 2000 (a total of 3 days). A Gram stain of a sputum sample obtained at baseline showed many white blood cells and moderate gram-positive cocci, but no pathogen was isolated from the culture. On 13 February 2000, the subject developed an ache on the right side of her chest. A chest x-ray performed on 15 February 2000 showed a right lower lobe infiltrate. A Gram stain of a sputum sample taken the same day showed gram-negative rods and many white blood cells. The culture grew *Pseudomonas aeruginosa.* The subject was hospitalized for pneumonia and treated with ceftazidime, tobramycin and levofloxacin. A chest x-ray performed on 24 February 2000 showed no infiltrate. The subject was discharged from the hospital on 27 February 2000. The subject completed treatment, but discontinued the study.

The subject had a past history of cataract surgery and hysterectomy, and a present history of chronic obstructive pulmonary disease, asthma, emphysema, congenital anomaly of the heart, right leg swelling, chronic sinusitis, sinus congestion, dyspepsia, headaches and difficulty sleeping. She was taking prednisolone acetate drops, prednisone, albuterol, triamcinolone, aspirin, multi-vitamins, temazepam, ipratropium and conjugated estrogens at the start of the study. Medications taken to treat the event are provided in the preceding paragraph.

In the opinion of the investigator, this event was due to other illness (suspected pseudomonal infection). Review by the applicant concluded the event was not related to azithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of failure at TOC.

B. Clarithromycin Treatment Group

Subject: 1013-245

This 73 year old White female subject weighing 62.6 kg was randomized on 31 March 00 to clarithromycin 1 Gm daily for the treatment of acute exacerbation of chronic obstructive bronchitis. Study drug was administered from 31 March 00 until 05 April 00. On 04 April 00, the subject was admitted to the hospital for exacerbation of chronic obstructive pulmonary disease (COPD) and pneumonia. On 05 April 00 the subject was discontinued from the study due to exacerbation of COPD. The pneumonia resolved on 11 April 00. The subject expired on 07 May 00 due to respiratory failure, COPD and semi-invasive aspergillosis. The investigator attributed the respiratory failure, COPD and pneumonia to the semi-invasive aspergillosis. The semi-invasive aspergillosis was attributed to steroid use and was unrelated to study drug.

The subject had a history of chronic obstructive pulmonary disease, atrial fibrillation, irritable bowel syndrome, cancer of the lungs, mild neuropathy, cataract removal, sinus congestion and dry mouth. Concomitant medications and routes of administration were as follows: albuterol, inhaled; levothyroxine, po; digoxin, po; phenytoin, po; verapamil, po; gabapentin, po; milk of magnesia, po; lorazepam, po; quinine sulfate, po; ipratropium, inhaled; salmeterol, inhaled; flovent, inhaled; vitamin E, po; vitamin C, po; multivitamin, po; calcium, po; and prednisone, po.

In the opinion of the investigator, the subject's death was due to respiratory failure, COPD and aspergillosis that were not related to study drug. Review within the company agrees with this assessment. The subject was not included in the MITT analysis of clinical response.

Subject: 1013-635

This 49-year-old Mulatto male subject weighing 58.0 kg received clarithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Clarithromycin was administered orally, bid, at a total daily dose of 1000 mg from 16 May 2000 until 26 May 2000, a total of 11 days. On 29 May 2000, the subject experienced a post-therapy event, bronchospasm, which was considered an important medical event. He had worsening dyspnea, cough, wheezing, coryza and a mild sore throat. A chest x-ray performed in the emergency room noted bilateral hyperinflation. The subject was treated with fenoterol, ipratropium bromide and aminophylline with good clinical response. He was discharged from the emergency room the same day. Fenoterol and amoxicillin treatment were prescribed. On 31 May 2000, the amoxicillin was discontinued and prednisone was started. The subject continued on fenoterol. A Gram stain done on 31 May 2000 showed > 25 WBC per LPF and bacterial organisms. Enterobacter species were isolated by sputum culture. The investigator attributed the >25 WBC to a viral upper respiratory tract infection, and the culture result to mixed flora not related to the respiratory tract infection. The event was considered resolved on 01 June 2000.

The subject has a present history of chronic bronchitis and moderate arterial hypertension. The subject took albuterol from Day 0 to Day 1. Medications taken to treat the event are provided in the preceding paragraph.

In the opinion of the investigator, this event was due to other illness (viral upper respiratory tract infection). Review by the applicant concluded the event was not related to clarithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC.**

Subject: 1013-640

This 64-year-old White female subject weighing 75.0 kg received clarithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Clarithromycin was

administered orally, bid, at a total daily dose of 1000 mg from 13 July 2000 until 23 July 2000, a total of 11 days. *Moraxella catarrhalis* was cultured at baseline and was susceptible to both azithromycin (MIC = 0.06 mcg/ml) and clarithromycin (MIC = 0.06 mcg/ml). On 07 August 2000 (visit 3 of the study), the subject reported that she wasn't feeling well over the weekend. She had a fever and left chest pain. The subject was taken to the emergency room. A chest x-ray performed on 07 August 2000 showed signs of COPD and pneumonia in the upper left lobe, hiatal hernia, enlarged cardiac area and increased aortic diameter. A sputum culture was positive for *Streptococcus pneumoniae,* which was susceptible to both azithromycin (MIC = 0.06 mcg/ml) and clarithromycin (MIC = 0.03 mcg/ml). An EKG showed sinus tachycardia (108 bpm) and diminished QT interval. She was diagnosed with bronchial pneumonia and was treated with oxygen and intravenous ampicillin/sulbactam. An x-ray done on 08 August 2000, showed parasinusitis, decreased transparency of ethmoidal cells in both sides and right frontal sinus and minimum enlargement of the soft tissues of the posterior wall of the rhinopharynx. Another chest x-ray was performed on 10 August 2000 and showed consolidation of the right lung and 2/3 of the lower left lung, interstitial edema, enlarged heart size and increased aortic diameter consistent with pneumonia and congestive heart failure. The subject was given clarithromycin and furosemide and was continued on ampicillin/sulbactam. The subject was discharged on 17 August 2000 with a prescription for clavulin, beserol and beclomethasone diproprionate. The pneumonia was considered resolved as of 14 September 2000 and the heart failure as of 25 September 2000.

The subject had a past history of chronic gastritis, cataract surgery, tubal ligation, varices, tonsillectomy, pneumonia and perineoplasty, and a present history of sinusitis, hiatal hernia, dizziness and menopause.The subject was taking aspirin, acetaminophen/carisoprodol/diclofenac and flunarizine at study entry and continued to take them during the study. Dipryone, caffeine/dipryone/orphenadrine, ampicillin, bemegride, acetaminophen and boric acid/retinal/vitamin D/zinc oxide were taken during the study.

In the opinion of the investigator, this event was due to other illness (bacterial infection). Review by the applicant concluded the event was not related to clarithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of failure at TOC.

Subject:1013-82

This 70-year-old White male subject weighing 84.1 kg received clarithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Clarithromycin was administered orally, bid, at a total daily dose of 1000 mg from 07 February 2000 until 17 February 2000, a total of 11 days. On 21 February 2000, during a follow-up examination, the subject was found to have severe dyspnea and was hospitalized for a left lower lobe infiltrate. On 02 March 2000, the subject was discharged to a rehabilitation unit and the event was considered resolved. The subject completed treatment, but discontinued the study.

The subject had a past history of coronary artery disease and a present history of chronic obstructive pulmonary disease [chronic bronchitis and chronic asthmatic bronchitis), hearing loss, allergies, insomnia, glaucoma, benign prostatic hypertrophy and depression. The subject was taking albuterol, aspirin, ipratropium, cetirizine, brimonidine, guaiphenesin, insulin, multivitamin/mineral mixture, fluticasone and theophylline at study entry and continued to take them during the study. Acetaminophen, tobramycin, cefotaxime, hydrocortisone, prednisone, vancomycin, piperacillin, mirtazapine and aminophylline were taken during the study.

In the opinion of the investigator, this event was due to (other) unknown cause, and not the study drug. Review by the applicant concluded the event was not related to clarithromycin. The subject was included in the MITT analysis of clinical response, with a final outcome of **failure at TOC**.

Subject: 1013-424

This 91-year-old White female subject weighing 52.0 kg received clarithromycin for the treatment of acute exacerbation of chronic obstructive bronchitis. Clarithromycin was administered orally, bid, at a total daily dose of 1000 mg on 01 August 2000, a total of 1 day. The clarithromycin treatment was discontinued because the subject did not meet inclusion criteria (subject's age exceeded inclusion criteria). On 04 August 2000, the subject was hospitalized due to pneumonia. A sputum sample taken on 01 August 2000 (when the subject was included in the study) showed abundant growth of *Haemophilus influenzae*. This infection was considered the cause of the pneumonia. The event was considered resolved on 11 August 2000, at which time the subject was discharged from the hospital. There is no available record of medications given during the subject's hospitalization.

The subject had a past history of uterine myoma (resulting in a total hysterectomy), cholecystitis and esophageal ulcers, and present history of anemia, arrhythmia, arthrosis and chronic bronchitis. The subject was taking nifedipine, aspirin, terbutaline, multivitamin/mineral mixture, amiodarone and thyroxine at study entry and continued to take them during the study.

In the opinion of the investigator, this event was due to (other) bacterial infection (*Haemophilus influenzae*). Review by the applicant concluded the event was not related to clarithromycin. The subject met the criteria for inclusion in the MITT analysis of clinical response, but did not have an outcome provided at end of therapy or test of cure because the subject was lost to follow-up.

APPENDIX V

DEATH NARRATIVES IN ISS

Narratives for Deaths That Occurred on Therapy or Within 35 Days Post Therapy

MO COMMENT: The following narratives for deaths in the ISS have been excerpted from the applicant's final study report. In general, deaths in the azithromycin treatment group did not appear related to the study drug. Review of the deaths that occurred in the comparator treatment group did not appear related to the study drug. (Note: The following narratives for deaths include only the narratives in the azithromycin group. The study protocol for each particular subject is specified before the subject ID number.)

Study AZM-CH-92-002; Subject ID # 31

This 33- year old white female subject in Switzerland received azithromycin for the treatment of pneumonia. Azithromycin was administered orally at a total daily dose of 500 mg on 29 September 1993, a total of 1 day. The subject was hospitalized on 29 September 1993 due to pneumonia of the middle lobe with fever and leukocytosis, and she received one dose of azithromycin (500 mg). On admission, the subject was in generally good condition and did not require oxygen. On 30 September 1993, the subject became hypotensive and experienced pulmonary insufficiency and required oxygen. Her condition continued to worsen, and the subject was moved to the ICU. Blood cultures from 29 September 1993 showed *Streptococcus pneumoniae* sensitive to erythromycin. Azithromycin treatment was permanently discontinued in order to begin IV antibiotic therapy with amoxicillin/clavulanic acid and erythromycin, and netilmicin. The next day, 01 October 1993, the subject had to be intubated due to increasing respiratory insufficiency (ARDS), and developed renal insufficiency. The subject also developed toxic cholangitis, probably as a result of the clavulanic acid, and antibiotic treatment was changed to imipenem. The subject's condition improved, but she still required intubation. On 19 October 1993, the fever reoccurred, increasing lung infiltrates were observed, and blood cultures showed coagulase-negative *Staphylococc*i. Treatment with ceftazidime and vancomycin was initiated, but bilateral infiltrates increased. On 20 October 1993, the subject had severe hypotension, was non-responsive to therapy, and died, with the cause of death reported as staphylococcal pneumonia and staphylococcal sepsis. According to the autopsy report, the subject died of pneumococcal sepsis, shock to organs (kidneys, liver, and lung), severe histio-lymphocytic myocarditis and fibrinous lymphocytic pericarditis, massive extramedullary erythro-leucopoiesis in spleen and lymph nodes with pseudolencemic reaction, and *Torulopsis glabrat*a-cystitis. The subject had a history of polytoxicomania (alcohol and benzodiazepine abuse) and bulimia. Concomitant therapy taken within two weeks prior to the onset of the event included doxycycline.

In the opinion of the investigator, these events were not likely due to azithromycin but to other illness (new pneumonia with staphylococci). Review by the applicant concluded the events were not related to azithromycin.

Study AZM-CH-92-002; Subject ID # 061

This 74-year-old white female subject in Switzerland received azithromycin for the treatment of pneumonia. Azithromycin was administered orally at a total daily dose of 500 mg from 03 February 1994 until 05 February 1994, a total of 3 days. The subject was hospitalized on 03 February 1994 for pneumonia. On 08 February 1994, three days after completing azithromycin treatment, her heart failure worsened. The following day, heart failure was confirmed by echocardiography. In addition, radiographs showed cardiomegaly, bilateral pleural effusion, and evidence of a possible pulmonary embolism. The subject's condition deteriorated rapidly. The subject did not respond to treatment, and on 18 February 1994, all medication was discontinued. On 20 February 1994, the subject died, with the cause of death reported as heart failure and suspected pulmonary embolism.

The subject had a history of heart failure and mild NIDDM. Concomitant therapy taken within two weeks before the onset of the event included spironolactone, enalapril, furosemide, digoxin, gliclazide, isosorbide dinitrate, nitroglycerin, and heparin.

In the opinion of the investigator, these events were not likely due to azithromycin but to other illness (heart failure). Review by the applicant concluded the events were not related to azithromycin.

Study AZM-CH-92-002; Subject ID# 71

This 53-year-old white male subject in Switzerland received azithromycin for the treatment of pneumonia. On 15 February 1994, the subject was hospitalized for increasing dyspnea and chronic obstructive pulmonary disease. Azithromycin was administered orally at a total daily dose of 500 mg from 15 February 1994 until 17 February 1994, a total of 3 days. Azithromycin treatment was completed. On 18 February 1994, the subject experienced increased dyspnea and sputum production. Azithromycin resistant *H. influenzae* was isolated in sputum and IV amoxicillin/clavulanic acid was initiated. Symptoms decreased within 48 hours. On 16 February 1994, during treatment with azithromycin, a left seropneumothorax occurred following drainage of a pleural effusion (1000 mL). During this procedure the subclavian vein was punctured and the subject experienced soft tissue emphysema. The subject was moved to the ICU and drainage was applied. The drain was removed on 27 February 1994 despite a residual pneumothorax. Also in February 1994, a bronchoscopy revealed metaplastic epithelial cells. On 09 March 1994, adenocarcinoma cells were found in the sputum and a diagnosis of lung cancer was made. On 11

March 1994, chest radiograph showed bilateral pleural effusions and alveolar infiltrate. The subject suffered from increasing dyspnea and died on 16 March 1994 from lung adenocarcinoma. The subject had a medical history of chronic obstructive pulmonary disease, coronary artery disease, depression, and peripheral arterial occlusive disease. Concomitant therapy taken within two weeks before the onset of the events included, nifedipine, aloxiprin, theophylline, nitroglycerin, prednisolone, formoterol, beclomethasone, ipratropium, and albuterol.

In the opinion of the investigator, these events were not likely due to azithromycin but to disease under study. Review by the applicant concluded the events were not related to azithromycin.

Study AZM-D-95-801; Subject ID # 46

This 71-year-old female subject of unknown race in Germany received azithromycin for the treatment of bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 11 March 1997 until 13 March 1997, a total of 3 days. Treatment was permanently discontinued because of lack of efficacy. On 13 March 1997, the subject was hospitalized because of worsening of acute infectious exacerbation of chronic bronchitis, status asthmaticus, respiratory insufficiency, and tachyarrhythmia absoluta. After temporary improvement, on 05 April 1997, the subject developed bronchial pneumonia, which led to septic shock, respiratory insufficiency, and circulatory failure. On 07 April 1997, she died, with the cause of death reported as septic shock. The subject had a past history of chronic obstructive lung disease. Concomitant therapy taken two weeks before the onset of the events included prednisolone, theophylline, salmeterol, and fluticason propionate.

In the opinion of the investigator, the events were not likely due to azithromycin but to disease under study. Review by the study sponsor concluded the events were not related to azithromycin.

Study AZM-NY-89-016B-801; Subject ID# 04

In Study AZM-NY-89-016B, subjects were to receive 500 mg/day azithromycin for 3 days. This 30-year-old black male subject in South Africa received azithromycin for the treatment of lobar pneumonia. On admission to the hospital, the subject was febrile, cyanotic, and semicomatose; blood and sputum cultures showed *Klebsiella pneumoniae*.The subject also had positive serology for Legionella. Azithromycin was administered orally at a total daily dose of 500 mg from 05 September 1990 until 06 September 1990, a total of 2 days. Oral azithromycin therapy was permanently discontinued because the subject was a protocol violator. The subject was treated by intubation and with IV penicillin, cefoxitin, and gentamicin. On 06 September 1990 (within 24 hours of admission to the hospital), the subject went into cardiac arrest. On 07 September 1990, the subject died with the cause of death reported as cardiac arrest and *Klebsiella* sepsis.

The subject had no known history of other illnesses that were present at the time of the onset of the event. Concomitant therapy taken within two weeks prior to the onset of the event included penicillin, cefoxitin, and gentamycin.

In the opinion of the investigator, this event was not likely due to azithromycin but to other events. Review by the study sponsor concluded the event was not related to azithromycin.

Study AZM-NY-89-017; Subject ID# 06

In Study AZM-NY-89-017, subjects were to receive 500 mg/day azithromycin for 3 days or 1,500 mg/day amoxicillin for 7 days. This 62-year-old white female subject in the UK received azithromycin for the treatment of lower respiratory tract infection secondary to chronic bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 16 February 1991 until 20 February 1991, a total of 5 days. Treatment with azithromycin was completed. Although the subject initially improved on azithromycin, on 20 February 1991, the subject experienced severe angina and a possible myocardial infarction. This progressed to cardiogenic shock with metabolic acidosis and ventilatory failure. The subject died on 23 February 1991. The cause of death was reported as respiratory failure, left ventricular failure, ischemic heart disease, bronchopneumonia, and chronic obstructive lung disease.

The subject had a history of ischemic heart disease, hypothyroidism, insomnia, left ventricular failure manifested by edema, and chronic obstructive airway disease. The subject also had a history of smoking, a myocardial infarction, and occasional angina. Concomitant medications taken within two weeks before the onset of the event included temazepam, thyroxine, nitroglycerin, albuterol, and bendrofluazide.

In the opinion of the investigator, these events were not likely due to azithromycin but to other illness (left ventricular failure). Review by the applicant concluded the events were not related to azithromycin.

Study Protocol AZM-NY-89-017; Subject ID# 12

In Study AZM-NY-89-017, subjects were to receive 500 mg/day azithromycin for 3-5 days or 1,500 mg/day amoxicillin for 7 days. This 80-year-old white male subject in the UK received azithromycin for the treatment of lower respiratory tract infection secondary to chronic bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 17 March 1991 until 22 March 1991, for a total duration of 6 days. The azithromycin treatment had been completed at the time of onset of the event. On 23 March 1991, the subject went into cardiac

arrest and died. The subject had a history of angina, chronic obstructive airway disease, osteoporotic wedge, myocardial infarction, and smoking. Concomitant therapy taken within two weeks before the onset of the event included ipratropium, albuterol, temazepam, codeine, and aminophylline.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (previous myocardial infarction and angina [ASCVD]). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-NY-89-017; Subject ID# 15

In Study AZM-NY-89-017, subjects were to receive 500 mg/day azithromycin for 3-5 days or 1,500 mg/day amoxicillin for 7 days. This 70-year-old white male subject in the UK received azithromycin for the treatment of bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 28 April 1991 until 02 May 1991, for a total duration of 5 days. Azithromycin treatment was completed. On 07 May 1991, the subject experienced an acute myocardial infarction and died. The subject had a history of smoking, ischemic heart disease, angina, chronic obstructive pulmonary disease, renal impairment, dyspepsia, and iron deficiency anemia. Concomitant therapy taken within two weeks before the onset of the event included isosorbide mononitrate, bumetanide, diltiazem, iron, nitroglycerin, nystatin, and ampicillin/flucloxacillin.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (heart disease). Review by the study sponsor concluded the event was not related to azithromycin.

Study Protocol AZM-NY-89-017; Subject ID# 20

In Study AZM-NY-89-017, subjects were to receive either 500 mg/day azithromycin for 3-5 days or 1,500 mg/day amoxicillin for 7 days. This 58-year-old white female subject in the UK received azithromycin for the treatment of a lower respiratory tract infection secondary to COAD. Azithromycin was administered orally at a total daily dose of 500 mg from 29 May 1991 until 02 June 1991, a total duration of treatment of 5 days. Although the subject's symptoms improved, on the night of 02 June 1991, the subject became agitated and was given 2.5 mg diamorphine to relieve respiratory distress. Ventilatory depression developed, and on 03 June 1991, 5 hours after the diamorphine dosing, the subject died. The cause of death was reported as respiratory arrest and cardiac arrest.

The subject had a history of severe chronic obstructive airways disease, acute exacerbation of chronic obstructive airways disease, TB, lung resection, and smoking. Concomitant therapy

taken within two weeks before the onset of the event included albuterol, ipratropium, temazepam, hydrocortisone, diamorphine, oxygen, and sulfamethoxazole/trimethoprim.

In the opinion of the investigator, these events were not likely due to azithromycin but to concomitant treatment/therapy (morphine). Review by the applicant concluded the events were not related to azithromycin.

MO Comment: Review of the CRF by the reviewer revealed that the investigator's assessment of the death of this patient was due to severe underlying respiratory disease.

Study Protocol AZM-NY-89-017; Subject ID# 43

In Study AZM-NY-89-017, subjects were to receive 500 mg/day azithromycin for 3 days or 1,500 mg/day amoxicillin for 7 days. This 74-year-old white female subject in the UK received azithromycin for the treatment of acute bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 26 February 1992 until 27 February 1992, a total duration of 2 days. The subject's condition improved on azithromycin, but on 28 February 1992 the subject experienced a myocardial infarction and died. As a result, treatment was discontinued. The cause of death was reported as progression of ischemic heart disease, acute myocardial infarction, and chronic obstructive airway disease.

The subject had a history of ischemic heart disease, previous myocardial infarction, and angina. Concomitant therapy taken two weeks before the onset of the event included aspirin, prednisolone, amitriptyline, albuterol, zopiclone, isosorbide mononitrate, hydrochlorothiazide/triamterene, verapamil, and nitroglycerin.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (ischemic heart disease). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-NY-90-001; Subject ID# 4

In Study AZM-NY-90-001, subjects were to receive 500 mg/day azithromycin for 3 days or 300 mg/day roxithromycin for 10 days. This 81-year-old white male subject in France received azithromycin for the treatment of lower respiratory tract infection. Azithromycin was administered orally at a total daily dose of 500 mg from 15 March 1991 until 17 March 1991, a total of 3 days. On 18 March 1991 the subject died due to respiratory failure secondary to chronic obstructive pulmonary disease. The subject had a history of chronic obstructive respiratory insufficiency, chronic bronchitis, and concurrent bronchial super infection.

Concomitant therapy taken two weeks before the onset of the event included furosemide, albuterol, methylprednisolone, fenoterol and beclomethasone.

In the opinion of the investigator, this event was not likely due to azithromycin but to disease under study. Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-NY-90-017; Subject ID# 242

In Study AZM-NY-90-017 subjects were to receive oral azithromcyin 500 mg bid on Day 1 and 500 mg qd on Days 2 to 5, IV benzyl penicillin 1,000,000 IU qid until 5 days after body temperature normalized, or oral erythromycin 500 mg qid for 10 days. This 72-year-old white male subject in Netherlands received azithromycin for the treatment of lobar pneumonia. Azithromycin was administered orally at a total daily dose of 500 mg from 01 October 1991 until 02 October 1991, a total of 2 days. On 02 October 1991, the subject died due to respiratory insufficiency secondary to pneumonia and bullous lung emphysema. Autopsy report noted that death was due to severe emphysema, pneumonia of lower left lobe, acute respiratory insufficiency, dyspnea, and possibly cardiogenic shock.The subject should not have been enrolled in the study because he had had a Bilroth II resection and dysphagia. However, the investigator was not aware of his condition at the time of enrollment. The subject had a history of very severe chronic obstructive pulmonary disease. He had bronchitis for 4 weeks prior to hospitalization which had progressed into pneumonia 6-7 days prior to death. The onset of pneumonia was estimated based on pathologic description of "white hepatization". In addition, the subject had a history of constipation, sleep disturbances, pulmonary fibrosis, possible carcinoma of the stomach, dehydration and cachexia. Concomitant therapy taken two weeks before the onset of the event included lactulose and temazepam.

In the opinion of the investigator, this event was not likely due to azithromycin but to disease under study. Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-NY-92-004; Subject ID # 03030048

In study AZM-NY-92-004 (double-dummy study), subjects were to receive either 500 mg/day azithromycin on Days 1-3 and amoxicillin/clavulanic acid placebo on Days 1-10, or 1875 mg/day amoxicillin/clavulanic acid and azithromycin placebo on Days 1-10. This 72-year-old white male subject in Belgium received azithromycin for the treatment of lower respiratory tract infection. Azithromycin was administered orally at a total daily dose of 500 mg on 10 December 1992 (duration of treatment up to onset of event was 12 hours). Later that day the subject developed possible cardiac arrythmia or mild cardiac infarction secondary to pre-existing heart disease and died. At the time of enrollment a chest radiogram was negative for pneumonia but positive for cardiomegaly and vascular overload. The ECG was consistent with arterial ischemia.

The subject had a history of bronchitis, smoking, hypertension, coronary artery bypass graft, hypercholesterolemia, hyperuricemia, angina, and depression. Concomitant therapy taken two weeks before the onset of the event included lisinopril, isosorbide dinatrate, dipyridamole, canrenoic acid, aspirin, benzbromarone, clotiazepam and ciprofibrate.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (heart disease). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-NY-92-004; Subject ID# 03340005

In study AZM-NY-92-004 (double-dummy study), subjects were to receive either 500 mg/day azithromycin on Days 1-3 and amoxicillin/clavulanic acid placebo on Days 1- 10, or 1875 mg/day amoxicillin/clavulanic acid and azithromycin placebo on Days 1- 10. This 81-year-old white male subject in Belgium received azithromycin for the treatment of exacerbation of chronic bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg starting on 10 February 1993. Treatment with azithromycin for 3 days was completed. The subject continued to receive amoxicillin/clavulanic acid placebo. On 15 February 1993, the amoxicillin/clavulanic acid placebo treatment was permanently discontinued due to drug resistance *(Morganella morganii)*. The subject experienced progression of infectious bronchitis and was treated with prefloxacin. However, he developed pneumonia as a complication of the chronic bronchitis and died on 27 February 1993. The cause of death was reported as exacerbation of chronic bronchitis.

The subject had a history of heart failure, supraventricular extra systoles, chronic bronchitis, gastric ulcer, cardiac decompensation, smoking, and deep venous thrombosis. Concomitant therapy taken two weeks before the onset of the event included flecainide, triamterene/epithiazide, furosemide, methylprednisolone, pefloxacine, ceftazidime, itraconazole, albuterol, phenprocoumon and ipratropium.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (pneumonia). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-NY-92-016; Subject ID # 03100228

In Study AZM-NY-92-016 (open-label comparative study), subjects were to receive either 500 mg/day azithromycin for 3 days or 750 mg/day cefaclor for 10 days. This 68-year-old white male subject in Ireland received azithromycin for the treatment of sinusitis. Azithromycin was administered orally at a total daily dose of 500 mg from 10 March 1993 until 12 March 1993, a

total of 3 days. The azithromycin treatment had been completed. On 17 March 1993, the subject died with the cause of death reported as myocardial infarction (acute).

The subject had a history of chronic obstructive pulmonary disease and anxiety. Concomitant therapy taken two weeks before the onset of the event included albuterol, beclomethasone, alprazolam and bromazepam.

In the opinion of the investigator, this event was not likely due to azithromycin but to other (myocardial infarction). Review by the study sponsor concluded the event was not related to azithromycin.

Study Protocol AZM-NY-93-007; Subject ID # 25

In study AZM-P-93-007, subjects were to receive 500 mg/day azithromycin for 3 days or 500 mg/day clarithromycin for 10 days. This 72-year-old white male subject in Portugal received azithromycin for an unknown indication. Azithromycin was administered orally bid at a total daily dose of 500 mg from 08 November 1995 until 10 November 1995, a total of 3 days. The azithromycin treatment had been completed. On 10 November 1995, the subject had a significant hemoptysis and died of progression of lung cancer.

The subject had a history of respiratory failure, chronic bronchitis and lung cancer. Concomitant therapy taken two weeks before the onset of the event included aminophylline, beclomethasone, heparin and albuterol/ipratropium.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (lung cancer). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-PAK-92-002A ; Subject ID # 13

In study AZM-PAK-92-002A, subjects were to receive 500 mg/day azithromycin for 3 days. This 49-year-old male subject in Pakistan received azithromycin for the treatment of suspected acute follicular tonsillitis. Azithromycin was administered orally daily at a total daily dose of 500 mg from 08 February 1994 until 09 February 1994, a total of 2 days. After 2 days, no response was seen and a whitish membrane developed on the tonsils uvula and pharyngeal wall. Diphtheria was suspected and study drug stopped. Alternative antibiotic treatment was begun, including penicillin and metronidazole. The subject was then found to have cellulitis of the neck and septicemia; the cardiologist confirmed the diagnosis of myocarditis. A lab test showed *Pseudomonas* spp. infection with intermediate sensitivity to azithromycin. On 11 February 1994, the subject developed respiratory distress and was treated with hydrocortisone, aminophylline,

oxygen, and tracheotomy. Subject died of cardiorespiratory failure on 12 February 1994. In the opinion of the investigator death was due to acute follicular tonsillitis.

The subject had no known other illnesses present at time of onset of event nor any other relevant medical history. Concomitant therapy taken within two weeks before the onset of the event included metronidazole and penicillin.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (acute follicular tonsillitis). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol AZM-SA-94-001; Subject ID # 4484

In study AZM-SA-94-001, subjects were to receive 500 mg/day azithromycin for 3 days. This 34-year-old Asian male subject in South Africa received azithromycin for the treatment of tonsillitis. Azithromycin was administered orally daily at a total daily dose of 500 mg from 03 March 1994 until 05 March 1994, a total of 3 days. On 12 March 1994, the subject died of a gunshot wound. The subject had no known illnesses present at time of onset of event nor any other relevant medical history. There were no known concomitant medications taken within two weeks before the onset of the event.

In the opinion of the investigator, this event was not likely due to azithromycin but to other (traumatic death by gunshot). Review by the applicant concluded the event was not related to azithromycin.

Study Protocol 066-326; Subject ID # 145-0081

In study 066-326 (a double-blind study) subjects were to receive either 500 mg/day azithromycin for 3 days or 500 mg amoxicillin every 8 hours for 5 days. This 66-year-old white male subject in Belgium received azithromycin for the treatment of bronchitis. Azithromycin was administered orally at a total daily dose of 500mg from 05 October 1988 until 07 October 1988, a total of 3 days. At the time of enrollment in the study, the subject had a urinary catheter in place because of preexisting prostatic hypertrophy. On 07 October 1988, the subject had a urinary hemorrhage which led to hypovolemic shock. Study drug was discontinued, but the subject died on 13 October 1988. The cause of death was considered to be hypovolemic shock, secondary to a urinary hemorrhage.

The subject had a history of peripheral vascular disease of the legs, vascular sclerosis, and prostatic hypertrophy. Concomitant therapy taken two weeks before the onset of the event included acetylcysteine and ipratropium.

In the opinion of the investigator, this event was not likely due to azithromycin, but to other causes. Review by the applicant concluded the event was not related to azithromycin.

Study Protocol 066-326 ; Subject ID # 157-0515

In Study 066-326 (a double-blind study) subjects were to receive either 500 mg/day azithromycin for 3 days or 500 mg amoxicillin every 8 hours for 5 days. This 77-year-old white male subject in Germany received azithromycin for the treatment of bronchitis. Azithromycin was administered orally at a total daily dose of 500mg from 08 February 1989 until 12 February 1989, a total of 5 days. Treatment with azithromycin was completed, and the subject was considered clinically cured. On 10 March 1989 the subject died with the cause of death reported as cardiac failure. No further details are available.

The subject had a history of bronchial carcinoma. There were no known concomitant medications taken two weeks before the onset of the event.

In the opinion of the investigator, this event was not likely due to azithromycin, but to other causes. Review by the study sponsor concluded the event was not related to azithromycin.

Study Protocol AZM-NY-90-017 ; Subject ID # 282

In study AZM-NY-90-017, subjects were to receive 500 mg/day azithromycin for 5 days, 500 mg/day erythromycin or 1,000,000 IU/day benzylpenicillin. This 68-year-old white male subject in the Netherlands received azithromycin for the treatment of lobar pneumonia. Azithromycin was administered orally at a total daily dose of 1000 mg on 27 December 1991 and orally at a total daily dose of 500 mg from 28 December 1991 until 31 December 1991, a total of 5 days. Cefuroxime was started 1 to 2 days after completion of azithromycin as the subject was still symptomatic. The subject was discharged, but was readmitted on 17 January 1992 with weight loss and fatigue. A diagnosis of Hodgkin's disease was made. On an unknown date the subject died with the cause of death reported as Hodgkin's disease.

The subject had a history of chronic obstructive pulmonary disease. Concomitant therapy taken two weeks before the onset of the event included albuterol and cefuroxime.

In the opinion of the investigator, this event was not likely due to azithromycin but to other illness (Hodgkin's disease). Review by the applicant concluded the event was not related to azithromycin.

APPENDIX VI - Narratives for Treatment-Related Serious Adverse Events in ISS (Azithromycin Treatment Group)

MO COMMENT: The following narratives for treatment-related serious AEs in the ISS have been excerpted from the applicant's final study report. Treatment-related serious AEs which occurred in nine subjects of the azithromycin treatment group appear to be possibly related to th study drug. Review of the treatment-related serious adverse events in the comparator groups revealed 3 subjects had events related to the study drug.

(Note: The following narratives for the serious AEs include only the narratives in the azithromycin group. The study protocol is specified before the subject ID number.)

Study Protocol AZM-NY-92-004; Subject ID # 151

In study AZM-NY-92-004 (double-dummy study), subjects were to receive either 500 mg/day azithromycin on Days 1-3 and amoxicillin/clavulanic acid placebo on Days 1-10, or 1875 mg/day amoxicillin/clavulanic acid and azithromycin placebo on Days 1-10. This 56-year-old white female in Belgium received azithromycin for the treatment of an acute lower respiratory tract infection. Azithromycin was administered orally at a total daily dose of 500 mg from 14 February 1994 to 17 February 1994, a total of 4 four days. On the fifth day (18 February 1994), the subject was discontinued from the study due to moderate nausea and vomiting. The case was considered serious because the subject's hospitalization was prolonged due to a persistent pathogen and intolerance of oral medications. Nausea and vomiting resolved on 19 February 1994. The subject was treated with IV amoxicillin/clavulanic acid from 18 February 1994 to 25 February 1994.

The subject had a history of gastric ulcer and chronic bronchitis. In addition to the amoxicillin/clavulanic acid, concomitant medications taken two weeks before the onset of the event included methylprednisolone.

In the opinion of the investigator, the events were most likely due to the azithromycin. Review by the applicant concluded that a relationship between the events and azithromycin could not be excluded.

Study Protocol AZM-PAK-96-001 ; Subject ID # 27

In study AZM-PAK-96-001, subjects were to receive 500 mg/day azithromycin for 3 days. This 17-year-old female subject in Pakistan received azithromycin for the treatment of acute tonsillitis, pharyngitis, and rhinitis. Azithromycin was administered orally at a total daily dose of 500 mg from 20 December 1996 to 22 December 1996, a total of 3 days. After 1 dose of azithromycin, the subject was admitted to the emergency room with severe pruritis, fever (103°F), and drowsiness. The subject was diagnosed as having an allergic reaction to the study drug. The subject was treated with an antihistamine and intravenous fluids. Study medication was continued unchanged, and the subject completed the study. No relevant medical history or concomitant medications were reported.

In the opinion of the investigator, the allergic events were due to the azithromycin, and the fever was most likely due to a progression of the disease under study and not related to the azithromycin. Review by the applicant concluded that the allergic events are compatible with a possible relationship to azithromycin. The fever was most likely due to a progression of the disease under study and was not related to the azithromycin.

Study Protocol AZM-S-91-001 ; Subject ID # 0051

In Study AZM-S-91-001 subjects were to receive either 500 mg/day azithromycin for 3 days or 1 g/day penicillin for 10 days. This 34-year-old white female subject in Sweden received azithromycin for the treatment of tonsillitis. Azithromycin was administered orally at a total daily dose of 500 mg from 18 November 1991 to 21 November 1991, a total of 4 days. On 07 February 1992, the subject donated blood and was found to have elevated LFTs. LFTs continued to increase over the next several months, and peaked in June-August 1992. The LFT data are summarized below:

ASAT/ALAT (Normal Range: <0.67 U kat/L); Total Bilirubin (Normal range = 3-20 μmol/L

- 7 February 1992 : ASAT = 0.87 ALAT = 1.5
- 26 February 1992: ASAT = 1.1 ALAT = 1.6
- 28 April 1992 : ASAT = 2.1 ALAT = 3.7
- 19 May 1992: ASAT = 2.6 ALAT = 6.1
- 2 June 1992 : Total bilirubin = 23 umol/L
- 15 June 1992: ASAT = 2.8 ALAT = 6.6
- 21 July 1992: ASAT = 0.93 ALAT = 1.8 ; Total bilirubin = 32 umol/L
- 24 August 1992: Total bilirubin = 41 umol/L
- 7 October 1992: Total bilirubin = 35 umol/L
- 10 November 1992: ASAT = 0.49 ALAT = 0.68 ; Total bilirubin = 30 umol/L

This event was considered to be serious because it required hospitalization. However, no hospitalization dates were noted. The probable cause of the LFT elevations was considered by the investigator to be Gilbert's syndrome and a late reaction to azithromycin. The condition was considered to be resolved on 10 November 1992, and was considered by the investigator to be related to azithromycin treatment. The subject had no relevant medical history, and received no concomitant therapy.

In the opinion of the investigator, these events were due to azithromycin. Review by the applicant concluded that a causal relationship between azithromycin and the symptoms was remote, but could not be ruled out.

Study Protocol AZM-S-91-001; Subject ID # 4121

In study AZM-SA-94-001, subjects were to receive 500 mg/day azithromycin for 3 days. This 33-year-old Asian male subject in South Africa received azithromycin for the treatment of pharyngitis. Azithromycin was administered orally at a total daily dose of 500 mg from 9 February 1994 until 11 February 1994. After receiving 2 doses of azithromycin for pharyngitis, the subject developed numbness in the legs and the penis, and a burning sensation in the lips. Azithromycin was permanently discontinued on 11 February 1994. Blistering of the lips and penis subsequently developed. A diagnosis of Steven's-Johnson syndrome was made, although no confirmatory laboratory or dermatology data are available. The event was considered resolved on 24 February 1994.

The subject had a history of Steven's-Johnson syndrome in reaction to acetaminophen and a penicillin allergy. Concomitant therapy included dimethindene-neomycin-phenylephrine, acetaminophen-caffeine-phenylephrine-chlorpheniramine, and Stopayne.

In the opinion of the investigator, this event was most likely due to azithromycin. Review by the applicant concluded the event was possibly related to azithromycin.

Study Protocol 066-326; Subject ID # 145-0170

In Study 066-326 (a double-blind study) subjects were to receive either 500 mg/day azithromycin for 3 days or 500 mg amoxicillin every 8 hours for 5 days. This 65-year-old white male subject in Belgium received azithromycin therapy for the treatment of bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 07 March 1989 to 09 March 1989, a total of 3 days. On 31 March 1989, the subject developed signs of cholestatic jaundice with "very" elevated levels of bilirubin, amylase, lipase, and alkaline phosphatase. A laparoscopy and a liver biopsy were performed on 07 April 1989. The biopsy showed modest accumulations of bile pigments with intracytoplasmic inclusions, bile thrombi, and enlarged and

edematous portal spaces. There was a nonspecific inflammatory infiltrate consisting of neutrophils, lymphocytes, and lymphoid cells. There were a few centrolobular fatty foci. The subject improved, but no final outcome or time course are available.

The subject had a history of osteoporosis, silicosis, esophagitis, chronic arthritis, respiratory insufficiency and erosions. Concomitant therapy taken two weeks before the onset of the event included ranitidine, theophylline, calcium salts, fluoride preparation, medigoxin, fenoterol, ipratropium, betamethasone, and acetylcysteine.

In the opinion of the investigator, this event was most likely due to azithromycin. Review by the applicant concluded the event was possibly related to azithromycin.

Study Protocol AZM-BRA-93-011; Subject ID# 1732-A

This 78-year-old white male subject in Brazil received azithromycin for the treatment of acute sinusitis. Azithromycin was administered orally at a total daily dose of 500 mg from 18 November 1993 until 19 November 1993, a total of 2 days. Azithromycin was permanently discontinued due to diarrhea, epigastralgia, nausea, and bloating. These events started between the first and second days of treatment, and resolved on 20 November 1993. The subject was hospitalized for these events, which were also considered to be life-threatening.

The subject had a history of hay fever and allergic bronchitis. No known concomitant therapy was taken two weeks before the onset of the event.

In the opinion of the investigator, this event was most likely due to azithromycin. Review by the study sponsor concluded that the event was possibly related to azithromycin.

Study Protocol AZM-A-94-001AB; Subject ID # 2734

This 81-year-old female of unknown race in Austria received azithromycin for the treatment of a respiratory tract infection. Azithromycin was administered orally at a total daily dose of 500 mg from 28 September 1994 to 30 September 1994, a total of 3 days. On 19 October 1994, the subject experienced a sudden loss of hearing in the left ear. The subject was referred to an otolaryngologist, who on 24 October 1994 gave a diagnosis of a significant deterioration of hearing due to labyrinthine deafness of the left ear, with pre-existing bilateral labyrinthine hearing impairment.

The subject had a history of cough. Concomitant therapy taken two weeks prior to the onset of the event included codeine and phenyltoloxamin.

In the opinion of the investigator, the event was most likely due to the azithromycin. Review by the applicant concluded that the event was not likely to be related to azithromycin because of the lack of a temporal relationship between the event and the azithromycin and also because the hearing loss occurred in only 1 ear.

Study Protocol AZM-A-94-001AB; Subject ID# 3404

In Study AZM-A-94-001AB, subjects were to receive 500 mg/day azithromycin for 3 days. This 6-month-old, 18 lb. male of unknown race in Austria received azithromycin for the treatment of otitis media. Azithromycin suspension was administered orally at a total daily dose of 10 mg/kg from 28 September 1994 to 30 September 1994, a total of 3 days. A perforated eardrum was noted on 04 October 1994, 4 days after treatment with azithromycin ended. No resolution date was provided.

The subject had a history of dentition. Concomitant therapy taken two weeks before the onset of the event included acetaminophen.
In the opinion of the investigator, the event was considered to be most likely due toazithromycin. Review by the applicant concluded that the event was not related to azithromycin but due to progression of the disease under study.

Study Protocol AZM-NY-90-018A; Subject ID # 65

In Study AZM-NY-90-018A, subjects were to receive either 500 mg/day azithromycin for 3 days or 1875 mg/day amoxicillin/clavulanic acid for 10 days. This 69-year-old white male subject in Netherlands received azithromycin for the treatment of chronic bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from 12 November 1991 to 15 November 1991, a total of 4 days. The subject developed a headache on 11 November 1991; on 14 November 1991, he developed nausea, vomiting, and upper abdominal pain, and was hospitalized. Study drug was permanently discontinued, and the events disappeared. Symptoms resolved by 17 November 1991. In the opinion of the investigator, the symptoms were study drug related. The subject had a history of hypothyroidism, hypertension, angina, edema, and COAD. Concomitant therapy taken within two weeks prior to the onset of the event included enalapril, albuterol, beclomethasone, theophylline, isosorbide dinitrate, thyroxine, furosemide, and prednisolone.

In the opinion of the investigator, these events were due to azithromycin. Review by the study sponsor concluded that a causal relationship could not be ruled out.

APPENDIX VII

Four-Month Safety Update

This 4-month safety update provides an incremental update of serious adverse events (including deaths) entered into the applicant's Adverse Event Monitoring Database (AEM) from October 26, 2000 (the day after the cutoff date for the sNDA) to the September 10, 2001 cutoff date for this submission. This Safety Update provides the serious AE data for subjects enrolled in clinical trials that employed a protocol defined regimen of azithromycin 500 mg/day for 3 days for the treatment of — AECB and
According to applicant, there was no attempt to exclude pediatric subjects who might have enrolled in these studies for this safety analysis.

There were six additional deaths entered into the AEM database as of September 10, 2001. All six subjects received azithromycin. Four deaths occurred while the subject was on therapy or within 35 days of the end of therapy and two occurred greater than 35 days post therapy. According to applicant, in no case did an investigator attribute a subject's death to azithromycin treatment.

According to the applicant, no new safety concerns have emerged since the submission of the sNDA.

The narrative summaries for the four deaths occurring on therapy or within 35 days post-therapy in the azithromycin group, are as follows:

MO COMMENT: The narratives are excerpted from the applicant's Information Amendment for the 4-month Safety Update (November 21, 2001). Review of the deaths that occurred during this period revealed that the causalities did not appear related to azithromycin therapy but due to the subject's other underlying diseases.

- Study Protocol A0661021

  Subject ID # 03006. This is a 70-year old Asian male in Japan who received azithromycin for the treatment of periodontitis. Azithomycin was administered orally at a total daily dose of 500 mg from May 18, 2001 until May 20, 2001, a total of 3 days. On May 20, 2001, the subject developed melena and a blood transfusion was given. On May 21, 2001, the subject died with the cause of death reported as rupture of esophageal varices and bleeding. The patient had a history of arrhythmia, diabetes, angina, gastroesophageal varices, hepatic cirrhosis, hypertension and rash. Concomitant therapy taken within two weeks before the onset of the event included spironolactone, cilazapril, furosemide, digoxin, isosorbide dinitrate, gliclazide, pilsicainide and aspirin aluminum.

In the opinion of the investigator, this event was due to other illness (esophageal varices). According to the applicant, the event was not related to azithromycin.

- Study Protocol A0661046

Subject ID # 0677. This is a 75-year old white male in Spain who received azithromycin for the treatment of exacerbation of chronic bronchitis. Azithromycin was administered orally at a total daily dose of 500 mg from December 4, 2000 until December 6, 2000, a total of 3 days. On January 08, 2001, the subject was hospitalized and died the following day due to acute respiratory insufficiency which according to the report of the investigator caused cardiac insufficiency. The subject had a history of arterial hypertension and benign prostatic hypertrophy. Concomitant therapy taken within two weeks before the onset of the event included acetylcysteine, formoterol, budesonide, theophylline, ipratropium, albuterol, amiloride/hydrochlorothiazide, finasteride and nimodipine.

In the opinion of the investigator, this event was due to another illness (acute respiratory insufficiency causing cardiac insufficiency). According to applicant, the event was not related to azithromycin.

- Study Protocol A0661048

Subject ID# 1001-001. This is a 68-year old Asian female in the Philippines who received azithromycin for the treatment of CAP. Azithromycin was administered intravenously at a total daily dose of 500 mg on July 25, 2001 (duration of treatment was 1 day) at approximately 3 pm. Seven hours later, the patient experienced a blood pressure spike of 180/110, HR of 96 and respiratory rate of 26. The patient's usual BP was reported as 160/70. Captopril was administered sublingually. Two hours later, a decreased sensorium was noted. Physical examination revealed that the patient was tachypneic, BP was 100/70, HR was in the range of 80-90 and oxygen saturation was 88%. The patient was subsequently intubated, given IV fluids and dopamine drip at 10 mg/kg/hr. The patient developed a cardiac arrest two hours later and advanced life support was provided. In the early morning of July 26, 2001, the patient died. The immediate cause of death was reported as cardiac failure secondary to probable acute myocardial infarction. According to the report, other significant conditions contributing to the subject's death were community-acquired pneumonia, suspected diabetes and hypertension. The patient had a history of sudden onset right-sided weakness, atrial fibrillation, inferolateral wall ischemia, new-onset CVA, prior CVA (in 1999) and hypertension stage III. Concomitant therapy taken within two weeks before the onset of the event included methyldopa, aspirin, digoxin, furosemide, captopril and citicoline.

According to the investigator, this event was due to other illness (cardiac failure secondary to myocardial infarction). The applicant concluded that the event was not related to azithromycin.

- Study Protocol A0661020

  Subject ID# 00030. This is a 72-year old male in France (race unknown) received azithromycin for the treatment of AECB. Azithromycin was administered orally at a total daily dose of 500 mg on June 2, 2001 and 250 mg from June 3, 2001 until June 6, 2001, a total of 5 days. A clinical examination report on June 8, 2001, revealed the subject to be in a good general state, no sweats, normal consciousness, HR of 64 beats/min, BP of 125/70, RR of 18/min, no crepitant focus, no cyanosis, a slight cough, slight chest pain and dyspnea. On June 30, 2001, the subject was found dead at home. The subject experienced a worsening of depression resulting in suicide. The subject had a history of cardiac rhythm disorder, arthrosis, primary tuberculosis, cataract surgery, surgery for air sinus, surgery for inguinal hernia, insomnia, bronchospasm, cigarette smoking (15 cigarettes/day), coronary heart disease and depression (starting 1983). Concomitant therapy taken within two weeks before the onset of the event included aspirin, diltiazem, amiodarone, nitroglycerin, acetaminophen/dextropropoxyphene, paroxetine, clorazepate/acepromazine/ aceprometazine, prednisone, enoxaparine and terbutaline.

  The investigator assessed the event was due to other illness (depression). The applicant concluded that the event was not related to azithromycin.

Review of Serious Adverse Events

Two hundred and thirty-two serious AE cases were included in the sNDA. Of the 232 cases, 113 occurred on azithromycin, 17 on blinded therapy and 102 on a comparator. An additional 65 serious AE cases have been entered into the AEM database as of September 10, 2001 cutoff data for this safety update. Of the 65 serious AE cases, 55 occurred on azithromycin, 5 on blinded therapy and 5 on a comparator. Four cases were attributed to azithromycin treatment by the investigator (narratives of the 4 cases are summarized below).

The most commonly reported (>2 events) serious AEs regardless of causality are summarized in the table below.

Table 1: Serious Advers Events in Phase 1-4 trials (>2 events in any treatment group) between October 26, 2000 and Septemebr 10, 2001

ADVERSE EVENT	AZITHROMYCIN	COMPARATOR	BLINDED THERAPY
Bronchitis	6	1	2
Bronchospasm aggravated	5	0	0
Pharyngitis	3	0	0
Pneumonia	6	0	2
Respiratory disorder	4	4	2

MO COMMENT: The most frequent serious AEs noted in the applicant's table above involved the respiratory system in the azithromycin and comparator groups. In general, these events appear to be related to the disease under study and not the direct effects of azithromycin. The outcome of all the events reported were resolved. These subjects were under study for upper and lower respiratory tract infections. The table has been modified as to its format by the reviewer.

Narratives for Treatment-Related Serious Adverse Events:

MO COMMENT: The following narratives for treatment-related serious AEs are excerpted from the applicant's four-month safety update. Review of the adverse events revealed that they were related to azithromycin therapy.

- Study Protocol A0661021;Subject ID# 02977

  This is a 46-year Asian male in Japan who received azithromycin for the treatment of acute pneumonia. Azithromycin was administered orally, once daily at a total daily dose of 500 mg from March 1, 2001 until March 3, 2001 (total 3 days). The azithromycin treatment had been completed. On March 8, 2001 the subject experienced hepatic dysfunction which was considered an important medical event. Neo-Minophagen C (Glycyrrhizin/Aminoacetic acid) was prescribed for treatment of the event. The event was considered resolved on March 27, 2001. The subject had a history of hypertension and hyperlipidemia. Concomitant therapy taken within two weeks before the onset of the event included teprenone, serrapeptase, dimemorfan, loxoprofen, povidone-iodine and panipenem/betamipron. The opinion of the investigator was that this event was due to azithromycin. The sponsor concluded that the event was not related to azithromycin.

  The liver function test (LFT) results for this subject are summarized in the table below:
  Note: The table has been modified as to its format by the reviewer.

Table 2: Summary of LFT Results

LFT	Reference Range	Results by Date			
		March 1, 2001	March 8 2001	March 15, 2001	March 27,2001
AST	8-40 IU/L	32	41	33	24
ALT	5-35 IU/L	35	105	68	31
ALP	77-278 IU/L	207	212	229	255
LDH	100-450 IU/L	345	282	251	314
GGTP	0-40 IU/L	16	17	24	18

AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase; LDH-lactate dehydrogenase; GGTP= gamma-glutamyl transferase

- Study Protocol A066102; Subject ID# 02977

  This is a 31-year old Asian male in Japan who received azithromycin for treatment of periodontitis. Azithromycin was administered orally, once daily, at a total dose of 500 mg on November 16, 2000, a total of 1 day. On that same day, the subject experienced vomiting which led to inpatient hospitalization. Azithromycin treatment was permanently discontinued due to the event. The event abated after azithromycin was discontinued. The event was considered resolved on Nov. 17, 2000.

  The subject had no known other illnesses at time of onset of event and no known relevant medical history according to the report. Concomitant therapy taken within two weeks before the onset of the event included loxoprofen sodium. This medication was also administered on Nov.16, 2000 and discontinued on that same day. The investigator's opinion of the event was that the event was due to azithromycin. The investigator also considered loxoprofen sodium treatment as related to the event. The sponsor concluded that the event was related to azithromycin.

- Study Protocol A0661021; Subject ID# 00497

  This is a 20-month Asian female in Japan who received Azithromycin for the treatment of otitis media. Azithromycin was administered orally, once daily, at a total daily dose of 100 mg from September 20, 2000 until September 22, 2000, a total of 3 days (completed azithromycin treatment). The patient experienced vomiting on Sept. 22, 2000 at post-therapy. This event led to inpatient hospitalization. The subject was treated with IV fluid and her condition improved. The patient was discharged from the hospital on Sept. 24, 2000. The event was reported as still present and considered better relative to onset. The patient had a history of upper respiratory infection. Concomitant therapy taken within two weeks before the onset of the event included carbocysteine. The investigator's opinion of this event was that it was due to azithromycin. The sponsor concluded that the event was related to azithromycin.

- Study Protocol A0661021; Subject ID# 00163

  This is a 15-month old Asian male in Japan who received Azithromycin for the treatment of pneumonia. Azithromycin was administered orally, once daily, at a total daily dose of 110 mg on August 15, 2000, a total of 1 day. On August 16, 2000, the patient experienced elevated hepatic enzymes. The patient had a temperature of 39.3°C on Aug.15. The following day, he had a temperature of 39.1°C. These events led to inpatient hospitalization. Azithromycin treatment was permanently discontinued due to the event. According to the report, the hospitalization was also for the treatment of pneumonia with intravenous antibiotics after discontinuation of azithromycin treatment. The event abated after azithromycin was discontinued. The event was considered resolved on August 30, 2000. The patient had no other known illnesses at time of onset of event and no known relevant medical

history. Concomitant therapy taken within two weeks before the onset of the event included clindamycin, fosfomycin and cefotiam. The investigator's opinion was that the event was due to azithromycin. The sponsor concluded that the event was related to azithromycin.

The relevant laboratory results for this subject are listed in the applicant's table below:
Note: The table has been modified as to its format by the reviewer.

Table 3: List of Laboratory Test Results

Lab test	Reference Range	Results by Date			
		Aug.15, 2000	Aug. 16 2000	Aug. 21, 2001	Aug. 30, 2000
WBC	4000-9500/μL	17, 100	17, 700	ND	ND
Neutrophil	48-61%	58	ND	ND	ND
AST	8-38 U/L	49	139	42	34
ALT	4-44 U/L	24	93	43	13
GGTP	16-73 U/L	ND	140	163	28
CRP	<0.5 mg/dL	8.3	6.5	ND	ND

WBC= white blood cells; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase; LDH-lactate dehydrogenase; GGTP= gamma-glutamyl transferase; CRP= C-reactive protein; ND=not done.

Conclusions:

Overall, the reported serious adverse events in this safety update for studies conducted by the applicant were related to gastrointestinal system. The serious treatment-related events were gastrointestinal in nature, being vomiting and elevated hepatic enzymes. These adverse events are already part of the label for azithromycin. These events resolved with discontinuation of azithromycin. The most frequent serious AEs, regardless of causality, reported in this Update were related to the respiratory system in studies for the upper and lower respiratory tract infections. In general, the four deaths reported in the azithromycin group were related to the subject's other diseases and were not attributed to azithromycin therapy.

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